UC Irvine

UC Irvine Previously Published Works

Title

Ten years of Nature Reviews Neuroscience: insights from the highly cited.

Permalink

<https://escholarship.org/uc/item/68c6m707>

Journal

Nature reviews. Neuroscience, 11(10)

ISSN

1471-003X

Authors

Luo, Liquan
Rodriguez, Eugenio
Jerbi, Karim
et al.

Publication Date

2010-10-01

DOI

10.1038/nrn2912

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Published in final edited form as:

Nat Rev Neurosci. 2010 October ; 11(10): 718–726. doi:10.1038/nrn2912.

Ten years of *Nature Reviews Neuroscience*: insights from the highly cited

Liqun Luo

Department of Biology, Howard Hughes Medical Institute, Stanford University, Stanford, California 94305, USA

Eugenio Rodriguez

Pontificia Universidad Catolica de Chile, San Joaquin, 8940000, Santiago, Chile, and the Max-Planck Institute for Brain Research, D60528 Frankfurt, Germany

Karim Jerbi

INSERM U821, Brain Dynamics and Cognition, Université Claude Bernard, Lyon 1, Lyon, France

Jean-Philippe Lachaux

INSERM U821, Brain Dynamics and Cognition, Université Claude Bernard, Lyon 1, Lyon, France

Jacques Martinerie

COGIMAGE, Université Pierre et Marie Curie–Paris 6, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Inserm, U975, CNRS, UMR 7225, Hôpital de la Salpêtrière, 75651 Paris, France

Maurizio Corbetta

Washington University School of Medicine, Saint Louis, Missouri 63110, USA

Gordon L. Shulman

Washington University School of Medicine, Saint Louis, Missouri 63110, USA

Daniele Piomelli

Department of Pharmacology, University of California, Irvine, California 92697, USA, and Unit of Drug Discovery and Development, Italian Institute of Technology, Genoa, 16163, Italy

Gina G. Turrigiano

Department of Biology and National Center for Behavioral Genomics, Brandeis University, Waltham, Massachusetts 02454, USA

Sacha B. Nelson

Department of Biology and National Center for Behavioral Genomics, Brandeis University, Waltham, Massachusetts 02454, USA

Marian Joëls

Department of Neuroscience & Pharmacology, Division of Neuroscience, Rudolf Magnus Institute, UMC Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands

E. Ronald de Kloet

Department of Medical Pharmacology, Leids Universitair Medisch Centrum (LUMC), Leiden–Amsterdam Center for Drug Research, P.O. BOX 9502, 2300 RA Leiden, The Netherlands

© 2010 Macmillan Publishers Limited. All rights reserved

Competing interests statement Daniele Piomelli is an inventor with several issued patents and patent applications pending covering aspects of endocannabinoid pharmacology. Robert Dantzer has received honorarium from Astra-Zeneca plc, Bristol-Myers Squibb plc and Lundbeck Laboratories. He is also a consultant for Lundbeck Laboratories. Keith W. Kelley has received honorarium from Astra-Zeneca plc. The remaining authors declare no competing financial interests.

Florian Holsboer

Max Planck Institute for Psychiatry, Kraepelinstrasse 2–10, 80804 Munich, Germany

David M. Amodio

Department of Psychology and the Center for Neural Science, New York University, New York, New York 10003, USA

Chris D. Frith

Center of Functionally Integrative Neuroscience, Aarhus University/Aarhus University Hospital, 8000 Århus C, Denmark, and the Wellcome Trust Centre for Neuroimaging, University College London, London WC1N 3BG, UK

Michelle L. Block

Department of Anatomy and Neurobiology, Virginia Commonwealth University Medical Campus, Richmond, Virginia 23298, USA

Luigi Zecca

Institute of Biomedical Technologies, Italian National Research Council, 20090 Segrate, Milano, Italy

Jau-Shyong Hong

Neuropharmacology Section, National Institute of Environmental Health Sciences, NIH Research Triangle Park, North Carolina 27709, USA

Robert Dantzer

Integrative Immunology and Behavior Program in the Department of Animal Sciences, College of Agricultural, Consumer and Environmental Sciences, and at the Department of Pathology, College of Medicine, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, USA

Keith W. Kelley

Integrative Immunology and Behavior Program in the Department of Animal Sciences, College of Agricultural, Consumer and Environmental Sciences, and at the Department of Pathology, College of Medicine, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, USA

A. D. (Bud) Craig

Atkinson Research Laboratory, Barrow Neurological Institute, Phoenix, Arizona 85013, USA

Abstract

To celebrate the first 10 years of *Nature Reviews Neuroscience*, we invited the authors of the most cited article of each year to look back on the state of their field of research at the time of publication and the impact their article has had, and to discuss the questions that might be answered in the next 10 years. This selection of highly cited articles provides interesting snapshots of the progress that has been made in diverse areas of neuroscience. They show the enormous influence of neuroimaging techniques and highlight concepts that have generated substantial interest in the past decade, such as neuroimmunology, social neuroscience and the 'network approach' to brain function. These advancements will pave the way for further exciting discoveries that lie ahead.

2000 Two decades of Rho GTPases**Liqun Luo**

In the early 1990s, the small GTPases Rho and Rac were discovered to be major regulators of the actin cytoskeleton in mammalian fibroblasts. Cell division cycle 42 (Cdc42), another member of the Rho GTPase family, was also identified as a key regulator of polarized growth during yeast budding. These classic studies¹ led to the hypothesis that Rho GTPases

are central players in the regulation of the morphogenesis of axons and dendrites in neurons². Indeed, this hypothesis was borne out by studies using dominant mutants — from insect to mammalian neurons — that supported the idea of an integral role for Rho GTPases in axonal, dendritic and spine morphogenesis. Given their central positions in intracellular signalling, Rho GTPases are poised to mediate the crucial link between extracellular factors that regulate the growth and guidance of neuronal processes, and the actin cytoskeleton. The 2000 Review published in this journal³ summarized the state of the field a decade ago, examining the neuronal morphogenetic processes that Rho GTPases regulate and the mechanisms by which Rho GTPases link upstream regulators to downstream cytoskeletal elements.

The last decade has witnessed an explosion in our knowledge about Rho GTPases in neurobiology. The proposed functions of Rho GTPases in neuronal morphogenesis were confirmed using loss-of-function mutants^{4,5}, but their functions have now been extended far beyond these initial studies. In addition to serving as central players in axon guidance and dendrite morphogenesis, Rho GTPases are now known to play important parts in neuronal polarity, neuronal migration, synapse formation, neurotransmitter receptor trafficking, stability of synaptic connections as well as of axonal and dendritic branches, axon regeneration after injury and axon myelination^{5,6}. Numerous positive regulators (RhoGEFs) and negative regulators (RhoGAPs) have been identified. A given organism usually has three to five times more genes encoding RhoGEFs and RhoGAPs than the number of Rho GTPases that they regulate⁷. Many RhoGEFs and RhoGAPs have been linked to receptors that receive extracellular signals, including guidance receptors to steer the axons during nervous system wiring and neurotransmitter receptors that regulate synapse formation and plasticity through activity-dependent processes. The downstream effector pathways, which were initially elucidated in non-neuronal cells, have been validated as having a role in different aspects of neuronal morphogenesis^{5,6}. Given the ubiquity of Rho GTPase involvement in neuronal development and function, it is not surprising that mutations in many genes encoding regulators and effectors of Rho GTPases cause human neurological disorders⁸. Rho GTPases and their regulators have been directly implicated in mental processes, such as memory and forgetfulness^{9,10}.

What lies ahead? The questions raised in the 2000 Review³ — what do Rho GTPases do, how do they achieve their functions and how are their activities regulated? — can now be answered with more clarity and sophistication. Given the vast number of Rho GTPases and their regulators that are often involved in regulating common processes, a systems biology perspective seems essential for providing a comprehensive understanding of their interrelationships. Additionally, developing ever-refined technologies for spatial and temporal examination and manipulation of the activities of Rho GTPases and their regulators *in vivo* will reveal more secrets of this fascinating class of proteins and will enrich our understanding of many different neurobiological processes.

2001 Brainweb 2.0: the quest for synchrony

Eugenio Rodriguez, Karim Jerbi, Jean-Philippe Lachaux and Jacques Martinerie

Over the last decade, the study of brain function has witnessed a pivotal change of focus from investigating the localization of specialized brain areas to investigation of spatially distributed functional networks. Our Review, published in this journal¹¹, was to become a hallmark of this paradigm shift. With something of a lucky prediction we entitled our paper 'The brainweb' not knowing that, 10 years later, the development of internet 2.0, web dynamics and small-world network theories would, more than ever, justify this title.

At the time of publication, our article was a pioneer in suggesting that, rather than relying on localized neural activity, the emergence of a unified cognitive act requires large-scale brain integration. We proposed that the most plausible mechanism that subserves the coordination of scattered mosaics of functionally specialized brain regions is the formation of dynamic links between neuronal assemblies, mediated by synchrony over multiple frequency bands. By driving home the idea that neural synchronization, a nonlinear neural property, can be assessed at multiple scales in micro, local and large-scale circuits, our 'brainweb' paper¹¹ was also instrumental in extending the original concept of neural synchrony from local feature binding¹² to large-scale cognitive integration¹³.

This set of ideas has evolved into numerous fundamental developments in recent years, including empirical efforts to directly assess the relations between neural activities at different spatial scales, which involve simultaneous recordings at multiple brain organization levels^{14,15}, and evidence for the participation of large-scale brain synchronization in conscious perception¹⁶. In addition, a large cohort of new methods has been proposed to be used to evaluate neural coordination. Some have applied non-invasive assessment of large-scale neural synchronization from sensor space to source space in an attempt to enhance anatomical precision and minimize volume-conduction effects^{17,18}. Other developments in functional connectivity tools include the use of cross-frequency synchronization measures^{19,20} and frequency flow analysis²¹. Measuring effective neural connectivity, which involves the estimation of causal effects in neural interactions, is also generating novel insights into large-scale brain dynamics²². Finally, novel general frameworks for the organization of the CNS have emerged through innovative theoretical models, such as the complexity model of consciousness²³, by conceptualizing neural circuits as a 'liquid state machine'²⁴ or by recent developments in quantitative analysis of complex networks based on graph theory²⁵.

As for the future, research into the functional role of long-range cortical coupling will most likely increasingly rely on stimulation techniques (both invasive and non-invasive) to artificially trigger or disturb cortical network dynamics. Unravelling the mechanisms of neural interaction at progressively finer spatiotemporal scales will also result from studies that bridge the gap between electrophysiological data and imaging connectivity studies. Future research will also evaluate neural synchronization in neurological and psychiatric disorders, with a double promise of shedding light on the functional role of neural communication in health and the exciting prospect of developing novel rehabilitation strategies. Finally, the use of inter-regional neural synchronization in brain-computer interfaces and real-time brain mapping applications²⁶ will result in efficient neural decoding, and single-trial data analysis will help to clarify the neural bases of cognitive function. Taken together, future studies will hopefully lead to a new theory relating multilevel self-organized brain activity to the emergence of mind and consciousness.

The outstanding research that has flourished following the publication of the 'brainweb' Review¹¹ 10 years ago is a beautiful tribute to a unique and visionary scientist. The inspiration of Francisco Varela (1946–2001) will live on through the highly promising findings that will no doubt continue to emerge in this field for many years to come.

2002 Attention networks: past, present and future

Maurizio Corbetta and Gordon L. Shulman

Attention is the mind's ability to focus on what is important (stimuli, thoughts, memories). An important early insight into the neural mechanisms of attention was the recognition that there is a separation between sources of attention — that is, dedicated neural systems for controlling information flow²⁷ — and the sites at which attention modulates sensory input,

such as the visual cortex. Neural recordings in monkeys in the 1980s to 1990s emphasized the dorso lateral prefrontal cortex as the main source of attention²⁸. However, beginning in the early 1990s, human neuroimaging studies showed that a different set of regions, more dorsally located in the frontal and posterior parietal cortex, were consistently recruited under conditions in which subjects selected the location or features of stimuli or the motor response relevant to a task, suggesting that these regions are an important source of attention. Our 2002 Review²⁹ highlighted the convergent evidence from neurophysiological, neuropsychological and neuroimaging observations that indicated the importance of a bilateral dorsal frontoparietal network as a source of goal-driven stimulus–response selection. We also introduced a second, ventral frontoparietal network that is lateralized to the right hemisphere and that is driven by the detection of stimuli, especially when stimuli are unattended (FIG. 1). The existence and function of this network were more speculative, particularly as little supporting evidence was available from the literature on monkeys. We were encouraged, however, by the anatomical overlap between the ventral network and lesions causing spatial neglect — a syndrome characterized by spatial and non-spatial deficits. We suggested, and later confirmed^{30,31}, that neglect reflects the combined dysfunction of both attention networks, with the ventral network being directly damaged by stroke and the dorsal network becoming impaired by disconnection from ventral regions.

An important discovery since our Review²⁹ was the identification of both ventral and dorsal networks in spontaneous activity under resting conditions³² (FIG.1), a strong indication that these attention networks constitute independent functional-anatomical entities, similarly to sensory and motor systems. Moreover, the role of the dorsal network as a principal source of top-down influence on the visual cortex was demonstrated using different methodologies^{33–36}. The phrase ‘stimulus-driven’ in our Review²⁹ led some to equate the ventral network with exogenous orienting, but we had already discussed a role of the dorsal network in guiding attention to salient sensory stimuli, and that unattended stimuli trigger responses in the ventral network based on their task relevance (that is, contingent orienting). The importance of the behavioural relevance of a stimulus for recruiting the ventral network, and of the dorsal network in exogenous orienting, has subsequently been strongly confirmed³⁷. Similarly, although the phrase ‘reorienting’ is sometimes equated with spatial reorienting, our Review²⁹ described how the ventral network is also recruited in ‘oddball’ paradigms that involve detection of stimuli with unexpected (and not necessarily spatial) features. Subsequent studies have further broadened the ‘reorienting’ functions of the ventral network to include stimulus-driven transitions between tasks and between task phases³⁷.

An important future question is how attentional signals in frontoparietal areas modulate spontaneous activity in visual areas³⁸. Answering this question will require reconciling models of attention with anatomical evidence of sparse feedforward thalamocortical connectivity³⁹ and with theories of brain function based on predictive coding^{40,41}. In addition, the dorsal frontoparietal network is not the origin of top-down signals for stimulus–response selection. It takes signals that encode task control, the expected value of stimuli and responses and knowledge from past experiences, and transforms them into a format that is appropriate for stimulus–response selection. However, the interaction of the dorsal network with networks that generate these input signals (task control, reward, long-term memory) is poorly understood. A more complete understanding of the functional interaction between attention networks and other brain systems, in healthy brains and in brain disorders, will crucially depend on combining functional MRI studies with electrophysiological (for example, electrocorticography (ECoG)) studies probing the time-frequency structure of neural activity.

2003 High expectations

Daniele Piomelli

The discovery of the endogenous cannabinoid system challenged conventional views about chemical neurotransmission. The main components of this system — a class of lipid molecules that mimic Δ^9 -tetrahydrocannabinol (Δ^9 -THC) in marijuana — serve key functions in the regulation of synaptic activity, yet they eschew some of the most basic rules of neurotransmission. The compounds, called endocannabinoids, are not stored in synaptic vesicles and do not transmit information from presynaptic to postsynaptic neurons, as most transmitters do. Rather, they are made on demand in membranes of postsynaptic cells and intervene in retrograde signalling processes in which information about postsynaptic activity flows back to nerve terminals.

The experiments that laid the groundwork for the current understanding of endocannabinoid neurobiology were published between 1988 and 2003, when cannabinoid receptors and their endogenous ligands were discovered^{42–44}, biochemical pathways for endocannabinoid metabolism were described^{45,46}, pharmacological and genetic tools to explore endocannabinoid physiology were developed and a role for the endocannabinoids as retrograde messengers was proposed⁴⁷. The 2003 article in *Nature Reviews Neuroscience*⁴⁸ provided an overview of those exciting findings and highlighted the distinction between endocannabinoid-mediated signalling and classical neurotransmission.

The scientific community was quick to recognize the novel features of endocannabinoid signalling and responded with a flurry of studies. Researchers delved into the molecular workings of the endocannabinoid system, searching for as-yet-unidentified receptors and ligands, probing the anatomical architecture of cannabinergic synapses, exploring the properties of endocannabinoid-metabolizing enzymes and uncovering physiological and pathological conditions in which endocannabinoid mechanisms might be involved. Thanks to those efforts, important progress has been made in understanding the functions served by the endocannabinoids in the control of brain development, energy balance, pain and stress-coping behaviour. Research has also brought into focus new questions, such as the separation of roles between different endocannabinoids and the functional significance of endocannabinoid signalling in peripheral tissues.

Like scientists in academia, drug hunters in the pharmaceutical industry reacted quickly to the discovery of the endocannabinoid system. They had long been interested in the analgesic properties of Δ^9 -THC, but the identification of endocannabinoid substances and their receptors revealed to them a variety of new targets for therapeutic intervention. Some researchers focused on developing receptor antagonists that could counteract the obesity-inducing effects that are attributed to endocannabinoid signals. Others took a diametrically opposite approach and concentrated on enhancing intrinsic endocannabinoid activity, either designing receptor agonists that could overcome the downsides of Δ^9 -THC (for example, the risk of producing abuse) or creating inhibitors that could interrupt endocannabinoid deactivation and magnify the normal analgesic and anti-stress actions of these messengers⁴⁹. Although preclinical and clinical data are still coming in, first tallies show that the latter strategy is most promising: the development of cannabinoid antagonists has been halted due to the high incidence of psychiatric side effects associated with these compounds, whereas cannabinoid agonists and endocannabinoid deactivation inhibitors are still moving forward in trials for the treatment of traumatic brain injury, pain and other disorders. More surprises, good and bad, are certainly ahead. Still, we should keep high our expectation that the endocannabinoids have yet to yield all their secrets and therapeutic opportunities.

2004 Homeostatic plasticity develops!

Gina G. Turrigiano and Sacha B. Nelson

In his classic work *The Wisdom of the Body*, the renowned physiologist Walter Cannon marvelled that:

somehow the unstable stuff of which we are composed has learned the trick of maintaining stability.⁵⁰

This trick is nowhere more astonishing than in the CNS where, somehow, despite their astronomical complexity, the circuits within our brains wire themselves up during development and manage to generate stable activity patterns throughout our lives. Although Claude Bernard and Walter Cannon (the 'fathers of homeostasis') long ago enshrined homeostatic regulation of key physiological parameters as a central tenet of physiology, it took a surprisingly long time for neurophysiologists to apply this thinking systematically to the understanding of neural circuits. Over the past roughly 15 years this has changed dramatically with the demonstration that neuronal firing is itself a key physiological parameter that is subject to homeostatic regulation and with the discovery of a family of homeostatic plasticity mechanisms that together keep neuronal firing within functional boundaries⁵¹. These include the regulation of intrinsic neuronal excitability through the modulation of ion channel number and function⁵² and the homeostatic regulation of synaptic strengths^{51,53}. Our 2004 Review⁵¹ came at a key moment for this nascent field and — by suggesting that homeostatic mechanisms are essential for proper circuit function — has played an inspirational role in driving research over the past 6 years.

Since 2004 the number of publications on homeostatic plasticity has grown exponentially, and major inroads are being made into uncovering the mechanisms that allow neurons to sense their activity and adjust synaptic and intrinsic parameters to keep it relatively constant^{54,55}. The functional consequences of homeostatic mechanisms for neural circuit development and plasticity are also under active investigation, in particular for synaptic scaling — one of the best understood forms of homeostatic synaptic plasticity. Synaptic scaling is the process that scales a neuron's synaptic strengths up or down to compensate for perturbations in average firing^{56,57}; because it works through global, proportional changes in all of a neuron's synaptic strengths, it is thought to enable neurons to stabilize firing without degrading the information that is stored in the synapse-specific changes in strength induced by Hebbian plasticity⁵¹. Synaptic scaling has been suggested to have roles in processes as diverse as the experience-dependent plasticity of sensory cortex^{51,55}, the generation of epileptic brain states⁵⁸ and the normalization of synaptic weights during sleep⁵⁹. Inroads into finding the underlying mechanisms are now generating tools that will allow investigators to selectively interfere with homeostatic mechanisms *in vivo* to precisely determine their role in normal physiology and disease. Investigators are continuing to uncover new adaptive plasticity mechanisms⁵⁴, and it seems likely that maintaining stability in neuronal activity is so crucial that there is a family of such mechanisms that operate over different temporal and spatial scales and that are differentially deployed by different cell types. Continuing studies in mammals and model organisms promise to reveal how adaptive mechanisms work in concert with Hebbian plasticity to confer both flexibility and stability to our brains.

2005 Stress and the brain: the sequel

Marian Joëls, E. Ronald de Kloet and Florian Holsboer

The message of our Review in 2005 (REF. 60) was twofold. Firstly, we argued that stress hormones, such as corticosteroids, coordinate responses of the body and the brain to achieve behavioural adaptation in the light of a stressful experience. These coordinated actions take

place via two closely related nuclear receptor types, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), localized in brain regions that are implicated in cognitive processing and emotional responses. Secondly, we proposed that an imbalance in these receptor-mediated actions renders predisposed individuals more vulnerable to mental disorders, such as major depression. Since then, major progress has been made in three fields: the molecular and cellular underpinnings of corticosteroid actions, functional connectivity underlying behavioural adaptation and identification of factors that may tip the balance from resilience to vulnerability in stress-related psychopathology.

With respect to the mechanism by which corticosteroids alter brain function, much more insight has been obtained in the molecular pathways that are affected by the hormones during basal ultradian rhythms and after stress, using advanced bio informatics⁶¹. In comparison to 'classical' neuro-transmitters, corticosteroid hormones have an enormous reach in their ability to change brain function, affecting functionally related gene pathways important for, for example, neurogenesis, neural plasticity and rhythmic processes, rather than individual genes. Moreover, it has become increasingly clear that corticosteroid receptors do not only act as powerful transcriptional regulators but also trigger rapid, non-genomic signals^{62,63}. This makes these hormones powerful agents, acting from seconds to minutes, blurring the rigid picture of fast-acting monoamines and peptides on the one hand and slower-acting steroid hormones on the other⁶⁴.

The functional connectivity within circuits that are affected by stress hormones in the rodent and the human brains, which involve the ventromedial prefrontal cortex, the amygdala and the hippocampus, is being rapidly elucidated with neuroimaging techniques combined with neurogenetic approaches^{65,66}. While genomic GR-mediated actions seem important for consolidation of relevant information, a hitherto unrecognized role of rapid MR-dependent actions has become clear in the switch from allocentric, hippocampal towards more egocentric, striatal learning strategies⁶⁷. This switch to habit-like learning strategies — which, it should be noted, are invaluable for survival in the short term — has also been observed after chronic stress in rodents⁶⁸.

When behavioural adaptation falls short, psychopathology may evolve. Much more has become known about genetic risk factors that contribute to the vulnerability or resilience of individuals to psychiatric disorders or to their responsiveness to pharmacotherapy. For example, genetic polymorphisms within *NR3C1*, the gene that encodes the GR, as well as polymorphisms in the gene encoding the GR co-chaperone FK506 binding protein 5 (*FKBP5*) (which have been shown to result in altered GR sensitivity) were reported to interact with early trauma to increase vulnerability for the development of depression and post-traumatic stress disorder^{69–70}. Interestingly, the same variants also predict a better response to antidepressant drug treatment^{71,72}.

Where from here? We anticipate that over the next years the relevance of nongenomic corticosteroid actions will not only be explored but also used to redirect brain activity and behaviour in individuals in whom endogenous hormone systems do not function adequately. This knowledge, combined with the genome-wide identification of susceptibility pathways of stress hormone action and with new insights in genetic vulnerability factors, will provide new biomarkers for stress-related brain disorders that may lead to personalized medical treatment of mental disorders.

2006 Meeting of minds: the medial frontal cortex and social cognition — 4 years on

David M. Amodio and Chris D. Frith

At the time of our Review⁷³, several studies had observed unique activations in medial prefrontal cortex (mPFC) regions in individuals when making judgments about people and their thoughts. Although researchers speculated that the mPFC might represent a special module for social cognition, the specific psychological processes represented by these activations were unclear.

Our goal was to provide a psychological account of these findings that integrated neuroanatomy and social psychology. Our theoretical model emphasized a domain-general function of the mPFC for representing information about goals and behaviours in the context of complex external contingencies (for example, social goals). Simply put, we proposed that the mPFC is involved in monitoring and acting on complex social goals⁷³.

Our Review has been cited often as a general review of the literature and also as a neuroanatomical analysis of the role of the mPFC in social cognition. But our main theoretical point — that the mPFC is involved in coordinating action on social goals — has received less attention. Indeed, the view that the mPFC is a specialized module for simple representations of the self and others persists despite the minimal correspondence that this characterization has with the anatomical and cognition literatures.

A major difficulty for the 'module' view is the baseline problem — the fact that mPFC areas associated with explicit thoughts about people are usually activated during resting periods. Our Review noted that during 'rest' periods in functional MRI studies, participants actually need to manage several tasks, such as maintaining instructions, dealing with anxiety and preparing for upcoming trials (not necessarily including self-reflection), which is consistent with our domain-general account of the mPFC⁷³. There have been a great many publications focused on resting state networks over the past 4 years, but there are still few attempts to discover what cognitive processes are actually occurring during rest (see REFS 74, 75 for two examples of such attempts).

Meanwhile, there have been considerable advances in our understanding of the connectivity and cognitive function of the human frontal cortex. For example, on the basis of connectivity, measured with diffusion tensor imaging (DTI), Beckmann *et al.*⁷⁶ identified a discrete region of the anterior cingulate cortex (cluster 3) in the vicinity of the paracingulate sulcus, which they linked to the region highlighted in our Review. With regard to cognitive function, the work of Koechlin and colleagues, demonstrating a hierarchical organization of frontal regions, is of particular relevance. In particular, the description by Koechlin and Hyafil⁷⁷ of a high-level mechanism for handling concurrent behavioural plans might usefully be applied to the handling of concurrent mental states of the self and others. Such an account is strongly consistent with our suggestion that the mPFC is not a dedicated social 'module' but rather has a domain-general function that enables the coordination of actions with social goals. Finally, computational accounts of mentalizing are now being developed; these accounts have identified the mPFC as a key player and specify much more precisely what its role may be⁷⁸.

2007 Microglia-mediated neurotoxicity and neurodegenerative disease

Michelle L. Block, Luigi Zecca and Jau-Shyong Hong

Microglia, the resident innate immune cells in the brain, are strongly implicated as a source of neuropathology in neurodegenerative diseases. Our 2007 Review⁷⁹ was designed to

delineate the mechanisms that are responsible for microglia-mediated neurotoxicity, and in it we presented evidence that microglia cause neuronal death when they are chronically activated⁷⁹. Specifically, we detailed the many, diverse triggers of microglial activation (for example, environmental toxins, endogenous disease proteins and neuronal damage) that converge onto a common neurotoxic pathway in microglia: reactive microgliosis and the chronic production of reactive oxygen species⁷⁹. In neurotoxic reactive microgliosis, the microglial response to neuronal injury culminates in a chronic, self-propelling cycle that fuels further neuronal damage and consequent microglial activation. This process has been emphasized as a common underlying factor in many neurodegenerative conditions.

Since our Review⁷⁹ the field has expanded exponentially. Neuron–microglia signals are now a major point of interest, with fractalkine^{80,81}, neuromelanin^{82,83}, μ -calpain⁸⁴, the macrophage 1 antigen receptor⁸⁵, CX3C chemokine receptor 1 (CX3CR1)⁸⁶ and purinergic receptors⁸⁷ having recently emerged as novel mediators of toxic reactive microgliosis. New reports indicate that, in addition to neuronal-injury signals and the microglial response to these signals, glial ageing^{88,89}, the blood-brain barrier⁹⁰ and systemic inflammation⁹¹ are key factors driving chronic, neurotoxic microglial activation in neurodegenerative disease. Yet, despite these scientific advances, the underlying, complex mechanisms of microglia pathology remain poorly understood.

As such, it is imperative that future research continues to explore the mechanisms of microglia-mediated neurotoxicity. Over the next several years, it remains of pressing importance for research to identify novel therapeutic targets for attenuating neurotoxic microglial activation in the hope of halting the progression of neurodegenerative disease. In addition, the sporadic nature of neurodegenerative diseases emphasizes a role for gene–environment interactions in disease aetiology. Thus, it is of urgent concern to identify the common environmental toxins that are culpable. Notably, air pollution has recently been highlighted as a potential culprit in neuroinflammation and CNS disease⁹², but the list of environmental compounds to consider is extensive. Furthermore, ageing is associated with reduced microglial turnover and reduced microglial lysosome activity, with consequent impairment of mitochondria recycling. These phenomena generate a population of aged microglia that overproduce cytokines and reactive oxygen species and induce neurodegeneration⁹³. This is a fundamental link between ageing and neurodegeneration and further inquiry is warranted.

Finally, because research points to a role for microglia early in neurodegenerative disease, future studies need to focus on the identification of markers and ligands with high sensitivity to specifically detect the conversion of microglia into the neurotoxic phenotype. This will allow for early detection of inflammation-mediated neurodegenerative diseases and a better understanding of the role of microglia in neuropathology. For example, preliminary *in vivo* imaging studies using a ^{11}C radioligand that binds to translocator protein (TSPO) show an affinity of this ligand for activated microglia that is higher than that of previous probes⁹⁴, but more specific *in vivo* imaging probes are needed. Alternatively, peripheral blood markers associated with neurodegenerative disease are already beginning to be identified. Given that increasing evidence links early peripheral inflammation to microglia-mediated neurotoxicity⁷⁹ and disease⁹⁵, exploring peripheral markers may be another realistic approach with considerable potential for translation to clinical practice.

In summary, the rate of recent advances in microglia biology makes this an extraordinary and exciting time in our field. Undoubtedly, as we continue to learn how microglia function both to promote CNS health and to have an active role in neuropathology, we will build on the insight and arsenal necessary to defend against the chronic cycle of microglia-mediated neurotoxicity.

2008 Inflammation, sickness and depression: before and after subjugation of the brain by the immune system

Robert Dantzer and Keith W. Kelley

The concept that the immune system talks to the brain to regulate a variety of behaviours was reinforced and extended in our Review published in 2008 (REF. 96). This article helped to solidify the concept that during a peripheral inflammatory event, the immune system subjugates the brain and holds it captive until the infection is cleared. There is nothing pathological about this because it is as important for the survival of the host as is the fear response to a dangerous threat. All this was already known when our Review was published⁹⁷. The true contribution of our Review was to go one step further, to propose a mechanism that could explain how a normally adaptive sickness response to a danger signal sensed by the immune system can go awry and lead to psychopathology in the form of major depressive disorders. At that time, systemic inflammation had already been identified as a possible causal factor in the development of major depressive disorders^{98,99}. However, clinical depression was viewed as simply a more prolonged and intense variant of sickness behaviour. We challenged this idea by proposing that although inflammation-induced depression develops on a background of sickness behaviour, the two conditions are different. Depression is mediated by a mechanism other than just the expression and action of proinflammatory cytokines in the brain. The molecular switch that promotes the transition from sickness to depression is activation of the tryptophan degrading enzyme, indoleamine 2,3-dioxygenase (IDO). This enzyme normally mediates the development of immunotolerance and resolution of an immune response by causing depletion of tryptophan from the local milieu and by producing cytotoxic metabolites, such as quinolinic acid¹⁰⁰. However, activation of the IDO pathway in the brain in response to a systemic immune response can lead to accumulation of neurotoxic metabolites, probably as a result of microglial and/or endothelial cell activation. Since our Review was published, a substantial amount of experimental evidence supporting a role for tryptophan metabolites in the pathophysiology of depression has accumulated^{101,102}. Once more, the concept itself was not totally new¹⁰³. However, the idea gained respectability because it has been tested in appropriate experimental designs in which sickness and depression-like behaviour can be dissociated.

There remain two very important aspects that are crucial for further progress in this adventure. The first is the application of the knowledge gained from studying behavioural responses to drastic inflammatory responses, to the symptoms that develop during milder and/or more chronic inflammatory states. Encouraging results have been obtained recently in experimental subjects submitted to typhoid vaccination¹⁰⁴ and in patients with breast cancer or cardiovascular diseases. The second crucial need is the development of new antidepressant drugs that target the brain immune system (for example, interleukin-1 production or action) or its secondary consequences (for example, activation of IDO or the enzymes responsible for degradation of kynurenine)¹⁰⁵. Whether such drugs will be useful for treating inflammation-associated depression and treatment-resistant depression will determine the ultimate success of what began as a case of subjugation.

2009 Increasing awareness in the insula

A. D. (Bud) Craig

The most cited article in *Nature Reviews Neuroscience* in 2009 was a Perspective in which I presented a succinct overview of an extraordinary convergence of recent findings across widely disparate fields of neuroscience. I proposed that these findings support the hypothesis that the (right and left) anterior insula engenders human subjective awareness¹⁰⁶. The

Perspective is cited frequently because this novel viewpoint provides a cogent and appealing explanation for the unexpected activation of the anterior insula (and the anterior cingulate) that investigators have reported in hundreds of functional imaging studies. The groundwork for this view was laid by a 2002 Perspective article, also highly cited¹⁰⁷, in which I described a phylogenetically novel pathway to the primate insular cortex that provides a homeostatic sensory representation of the physiological condition of the body, and that leads to re-representations in the anterior insula that underlie human awareness of affective feelings, consistent with the James–Lange theory of emotion¹⁰⁸ and the 'somatic marker' hypothesis¹⁰⁹. The 2009 Perspective¹⁰⁶ suggested, based on recent neuroimaging findings, that this pathway involves an evolutionary progression of increasingly energy-efficient homeostatic re-representations extending from the posterior to anterior insula that successively incorporate all neural activity, an idea that is consistent with the social brain hypothesis¹¹⁰ and the recognition that energy utilization is a crucial arbiter of brain evolution¹¹¹.

Before these articles, all sensations and feelings from the body were thought to be routed through the Rolandic somato-sensory cortex, and discussions of human consciousness featured connectional networks involving the entire cerebral cortex or speculative quantum mechanical interactions. Moreover, the insula was usually regarded as an allocortical (or archaic) deep brain structure that is related to the amygdala and visceromotor function; furthermore, because it hides beneath the overlying opercular folds of the parietal and temporal lobes, the insula was quite often simply ignored. Ten years before the 2009 Perspective¹⁰⁶, to the best of my knowledge, no authors had considered the possibility that consciousness might be substantiated by the insular cortex.

The 2009 Perspective¹⁰⁶ led immediately to the recruitment of authors for a special issue on the insula in a specialized functional anatomical journal¹¹², in which leading investigators from different neuroscience fields could re-appraise their field from the new perspective afforded by the extraordinary convergence of evidence about the anterior insula. The ideas generated by the 2009 Perspective¹⁰⁶ will certainly guide new imaging and morphometry studies on the neural bases of mood disorders (anxiety and depression), schizophrenia, the forebrain asymmetry of positive and negative emotions, subjective time perception, music appreciation, meditation, somatization syndromes, focal attention, risk and error processing, and so on, because the insula is involved in all human feelings and behaviours. In order to address the functions of the insula, new techniques for combining imaging and electrophysiological recordings will be needed, perhaps involving patients with ecstatic epileptic seizures¹¹³. Future studies of insula function will enable deep insights into the neural basis for subjectivity, volition, individual personality and self-modulation.

Acknowledgments

L.L. thanks support from the National Institutes of Health (NIH) and the Howard Hughes Medical Institute. E.R. was partly supported by the Comisión Nacional de Investigación Científica y Tecnológica and the Deutscher Akademischer Austauschdienst. K.J. and J.P.L. were partly supported by the Fondation pour la Recherche Médicale and by the BrainSync FP7 European Project (grant HEALTH-F2-2008-200728). M.C. and G.L.S. thank S. Astafiev for assistance with figure 1. D.P. gratefully acknowledges support from the National Institute on Drug Abuse and the National Alliance for Research on Schizophrenia and Depression. G.G.T. and S.B.N. thank all members of their laboratories, past and present, as well as the many colleagues and collaborators who have contributed to the genesis of their ideas. E.R.d.K. gratefully acknowledges the support of the Royal Academy of Arts and Sciences (KNAW). D.M.A. is supported by grant BCS 0847350 from the American National Science Foundation and C.D.F. is supported by the Danish National Research Foundation. M.L.B. was supported by the National Institute of Environmental Health Sciences (NIEHS)/NIH Outstanding New Environmental Scientist Award (grant R01ES016951). L.Z. was supported by the Lombardia Region Department of Industry, Project Metadistretti. J.-S. H. was partly funded by the Intramural Research Program of the NIEHS (part of the NIH). K.W.K. is supported by the NIH (grant R01 AG 029573) and R.D. is supported by the NIH (grant R01 MH 079829). A.D.C. is grateful to the James S. McDonnell Foundation and to the Barrow Neurological Foundation.

References

1. Hall A. Rho GTPases and the actin cytoskeleton. *Science*. 1998; 279:509–514. [PubMed: 9438836]
2. Luo L, Liao YJ, Jan LY, Jan YN. Distinct morphogenetic functions of similar small GTPases: *Drosophila* Drac1 is involved in axonal outgrowth and myoblast fusion. *Genes Dev*. 1994; 8:1787–1802. [PubMed: 7958857]
3. Luo L. Rho GTPases in neuronal morphogenesis. *Nature Rev. Neurosci*. 2000; 1:173–180. [PubMed: 11257905]
4. Ng J, et al. Rac GTPases control axon growth, guidance and branching. *Nature*. 2002; 416:442–447. [PubMed: 11919635]
5. Heasman SJ, Ridley AJ. Mammalian Rho GTPases: new insights into their functions from *in vivo* studies. *Nature Rev. Mol. Cell Biol*. 2008; 9:690–701. [PubMed: 18719708]
6. Govek EE, Newey SE, Van Aelst L. The role of the Rho GTPases in neuronal development. *Genes Dev*. 2005; 19:1–49. [PubMed: 15630019]
7. Billuart P, Winter CG, Maresh A, Zhao X, Luo L. Regulating axon branch stability: the role of p190 RhoGAP in repressing a retraction signaling pathway. *Cell*. 2001; 107:195–207. [PubMed: 11672527]
8. Nadif Kasri N, Van Aelst L. Rho-linked genes and neurological disorders. *Pflugers Arch*. 2008; 455:787–797. [PubMed: 18004590]
9. Lamprecht R, Farb CR, LeDoux JE. Fear memory formation involves p190 RhoGAP and ROCK proteins through a GRB2-mediated complex. *Neuron*. 2002; 36:727–738. [PubMed: 12441060]
10. Shuai Y, et al. Forgetting is regulated through Rac activity in *Drosophila*. *Cell*. 2010; 140:579–589. [PubMed: 20178749]
11. Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. *Nature Rev. Neurosci*. 2001; 2:229–239. [PubMed: 11283746]
12. Gray CM, König P, Engel AK, Singer W. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature*. 1989; 338:334–337. [PubMed: 2922061]
13. Rodriguez E, et al. Perception's shadow: long-distance synchronization of human brain activity. *Nature*. 1999; 397:430–433. [PubMed: 9989408]
14. Whittingstall K, Logothetis NK. Frequency-band coupling in surface EEG reflects spiking activity in monkey visual cortex. *Neuron*. 2009; 64:281–289. [PubMed: 19874794]
15. Dalal SS, et al. Simultaneous MEG and intracranial EEG recordings during attentive reading. *Neuroimage*. 2009; 45:1289–1304. [PubMed: 19349241]
16. Melloni L, et al. Synchronization of neural activity across cortical areas correlates with conscious perception. *J. Neurosci*. 2007; 27:2858–2865. [PubMed: 17360907]
17. Cosmelli D, et al. Waves of consciousness: ongoing cortical patterns during binocular rivalry. *Neuroimage*. 2004; 23:128–140. [PubMed: 15325359]
18. Jerbi K, et al. Coherent neural representation of hand speed in humans revealed by MEG imaging. *Proc. Natl Acad. Sci. USA*. 2007; 104:7676–7681. [PubMed: 17442753]
19. Palva JM, Palva S, Kaila K. Phase synchrony among neuronal oscillations in the human cortex. *J. Neurosci*. 2005; 25:3962–3972. [PubMed: 15829648]
20. Canolty RT, et al. High γ power is phase-locked to theta oscillations in human neocortex. *Science*. 2006; 313:1626–1628. [PubMed: 16973878]
21. Rudrauf D, et al. Frequency flows and the time-frequency dynamics of multivariate phase synchronization in brain signals. *Neuroimage*. 2006; 31:209–227. [PubMed: 16413209]
22. Gregoriou GG, Gotts SJ, Zhou H, Desimone R. High frequency, long-range coupling between prefrontal and visual cortex during attention. *Science*. 2009; 324:1207–1210. [PubMed: 19478185]
23. Tononi G. An information integration theory of consciousness. *BMC Neurosci*. 2004; 5:42. [PubMed: 15522121]
24. Maass W, Natschläger T, Markram H. Real-time computing without stable states: a new framework for neural computation based on perturbations. *Neural Comput*. 2002; 11:2531–2560. [PubMed: 12433288]

25. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Rev. Neurosci.* 2009; 10:186–198. [PubMed: 19190637]
26. Lachaux JP, et al. A blueprint for real-time functional mapping via human intracranial recordings. *PLoS ONE.* 2007; 2:e1094. [PubMed: 17971857]
27. Posner MI, Petersen SE. The attention system of the human brain. *Annu. Rev. Neurosci.* 1990; 13:25–42. [PubMed: 2183676]
28. Desimone R, Duncan J. Neural mechanisms of selective visual attention. *Annu. Rev. Neurosci.* 1995; 18:193–222. [PubMed: 7605061]
29. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nature Rev. Neurosci.* 2002; 3:201–215. [PubMed: 11994752]
30. Corbetta M, et al. Neural basis and recovery of spatial attention deficits in spatial neglect. *Nature Neurosci.* 2005; 8:1603–1610. [PubMed: 16234807]
31. He BJ, et al. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron.* 2007; 53:905–918. [PubMed: 17359924]
32. Fox MD, et al. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc. Natl Acad. Sci. USA.* 2006; 103:10046–10051. [PubMed: 16788060]
33. Moore T, Armstrong KM. Selective gating of visual signals by microstimulation of frontal cortex. *Nature.* 2003; 421:370–373. [PubMed: 12540901]
34. Ruff CC, et al. Concurrent TMS-fMRI and psychophysics reveal frontal influences on human retinotopic visual cortex. *Curr. Biol.* 2006; 16:1479–1488. [PubMed: 16890523]
35. Bressler SL, et al. Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *J. Neurosci.* 2008; 28:10056–10061. [PubMed: 18829963]
36. Capotosto P, Babiloni C, Romani GL, Corbetta M. Frontoparietal cortex controls spatial attention through modulation of anticipatory α rhythms. *J. Neurosci.* 2009; 29:5863–5872. [PubMed: 19420253]
37. Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. *Neuron.* 2008; 58:306–324. [PubMed: 18466742]
38. Mitchell JF, Sundberg KA, Reynolds JH. Spatial attention decorrelates intrinsic activity fluctuations in macaque area V4. *Neuron.* 2009; 63:879–888. [PubMed: 19778515]
39. Douglas RJ, Martin KA. Mapping the matrix: the ways of neocortex. *Neuron.* 2007; 56:226–238. [PubMed: 17964242]
40. Rao RP, Ballard DH. Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nature Neurosci.* 1999; 2:79–87. [PubMed: 10195184]
41. Friston K. Beyond phrenology: what can neuroimaging tell us about distributed circuitry? *Annu. Rev. Neurosci.* 2002; 25:221–250. [PubMed: 12052909]
42. Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. *Mol. Pharmacol.* 1988; 34:605–613. [PubMed: 2848184]
43. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature.* 1990; 346:561–564. [PubMed: 2165569]
44. Devane WA, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science.* 1992; 258:1946–1949. [PubMed: 1470919]
45. Di Marzo V, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature.* 1994; 372:686–691. [PubMed: 7990962]
46. Stella N, Schweitzer P, Piomelli D. A second endogenous cannabinoid that modulates long-term potentiation. *Nature.* 1997; 388:773–778. [PubMed: 9285589]
47. Alger BE. Retrograde signaling in the regulation of synaptic transmission: focus on endocannabinoids. *Prog. Neurobiol.* 2002; 68:247–286. [PubMed: 12498988]
48. Piomelli D. The molecular logic of endocannabinoid signalling. *Nature Rev. Neurosci.* 2003; 4:873–884. [PubMed: 14595399]
49. Di Marzo V. Targeting the endocannabinoid system: to enhance or reduce? *Nature Rev. Drug Discov.* 2008; 7:438–455. [PubMed: 18446159]

50. Cannon, WB. *The Wisdom of the Body*. W. W. Norton Co. Inc; New York: 1932.
51. Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. *Nature Rev. Neurosci.* 2004; 5:97–107. [PubMed: 14735113]
52. Marder E, Goaillard JM. Variability, compensation and homeostasis in neuron and network function. *Nature Rev. Neurosci.* 2006; 7:563–574. [PubMed: 16791145]
53. Davis GW, Bezprozvanny I. Maintaining the stability of neural function: a homeostatic hypothesis. *Annu. Rev. Physiol.* 2001; 63:847–869. [PubMed: 11181978]
54. Pozo K, Goda Y. Unraveling mechanisms of homeostatic synaptic plasticity. *Neuron.* 2010; 66:337–351. [PubMed: 20471348]
55. Turrigiano GG. The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell.* 2008; 135:422–435. [PubMed: 18984155]
56. Ibata K, Sun Q, Turrigiano GG. Rapid synaptic scaling induced by changes in postsynaptic firing. *Neuron.* 2008; 57:819–826. [PubMed: 18367083]
57. Turrigiano GG, et al. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature.* 1998; 391:892–896. [PubMed: 9495341]
58. Houweling AR, et al. Homeostatic synaptic plasticity can explain post-traumatic epileptogenesis in chronically isolated neocortex. *Cereb. Cortex.* 2005; 15:834–845. [PubMed: 15483049]
59. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res. Bull.* 2003; 62:143–150. [PubMed: 14638388]
60. de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. *Nature Rev. Neurosci.* 2005; 6:463–475. [PubMed: 15891777]
61. Goeman JJ, van de Geer SA, de Kort F, van Houwelingen HC. A global test for groups of genes: testing association with a clinical outcome. *Bioinformatics.* 2004; 20:93–99. [PubMed: 14693814]
62. Karst H, et al. Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proc. Natl Acad. Sci. USA.* 2005; 102:19204–19207. [PubMed: 16361444]
63. Karst H, Berger S, Erdmann G, Schütz G, Joëls M. Metaplasticity of amygdalar responses to the stress hormone corticosterone. *Proc. Natl Acad. Sci. USA.* 2010; 107:14449–14454. [PubMed: 20663957]
64. Joëls M, Baram TZ. The neuro-symphony of stress. *Nature Rev. Neurosci.* 2009; 10:459–466. [PubMed: 19339973]
65. Rasch B, et al. A genetic variation of the noradrenergic system is related to differential amygdala activation during encoding of emotional memories. *Proc. Natl Acad. Sci. USA.* 2009; 106:19191–19196. [PubMed: 19826083]
66. Cousijn H, et al. Acute stress modulates genotype effects on amygdala processing in humans. *Proc. Natl Acad. Sci. USA.* 2010; 107:9867–9872. [PubMed: 20457919]
67. Schwabe L, Schächinger H, de Kloet ER, Oitzl MS. Corticosteroids operate as a switch between memory systems. *J. Cogn. Neurosci.* 2010; 22:1362–1372. [PubMed: 19445601]
68. Dias-Ferreira E, et al. Chronic stress causes frontostriatal reorganization and affects decision-making. *Science.* 2009; 325:621–625. [PubMed: 19644122]
69. Bet PM, et al. Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: new evidence for a gene-environment interaction. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2009; 150B:660–669. [PubMed: 19051288]
70. Binder EB, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA.* 2008; 299:1–15.
71. Binder EB, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nature Genet.* 2004; 36:1319–1325. [PubMed: 15565110]
72. Van Rossum EF, et al. Polymorphisms of the glucocorticoid receptor gene and major depression. *Biol. Psychiatry.* 2006; 59:681–688. [PubMed: 16580345]
73. Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nature Rev. Neurosci.* 2006; 7:268–277. [PubMed: 16552413]

74. Christoff K, et al. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc. Natl Acad. Sci. USA*. 2009; 106:8719–8724. [PubMed: 19433790]
75. Delamillieure P, et al. The resting state questionnaire: an introspective questionnaire for evaluation of inner experience during the conscious resting state. *Brain Res. Bull.* 2010; 81:565–573. [PubMed: 20003916]
76. Beckmann M, Johansen-Berg H, Rushworth MF. Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J. Neurosci.* 2009; 29:1175–1190. [PubMed: 19176826]
77. Koechlin E, Hyafil A. Anterior prefrontal function and the limits of human decision-making. *Science*. 2007; 318:594–598. [PubMed: 17962551]
78. Behrens TE, Hunt LT, Rushworth MF. The computation of social behavior. *Science*. 2009; 324:1160–1164. [PubMed: 19478175]
79. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nature Rev. Neurosci.* 2007; 8:57–69. [PubMed: 17180163]
80. Shan S, et al. NEW evidences for fractalkine/CX3CL1 involved in substantia nigral microglial activation and behavioral changes in a rat model of Parkinson's disease. *Neurobiol. Aging*. Apr 14.2009 doi:10.1016/j.neurobiolaging.2009.03.004.
81. Cardona AE, et al. Control of microglial neurotoxicity by the fractalkine receptor. *Nature Neurosci.* 2006; 9:917–924. [PubMed: 16732273]
82. Zhang W, et al. Neuromelanin activates microglia and induces degeneration of dopaminergic neurons: implications for progression of Parkinson's disease. *Neurotox. Res.* Dec 3.2009 (doi: 10.1007/s12640-009-9140-z).
83. Sulzer D, et al. Neuronal pigmented autophagic vacuoles: lipofuscin, neuromelanin, and ceroid as macroautophagic responses during aging and disease. *J. Neurochem.* 2008; 106:24–36. [PubMed: 18384642]
84. Levesque S, et al. Reactive microgliosis: extracellular micro-calpain and microglia-mediated dopaminergic neurotoxicity. *Brain*. 2010; 133:808–821. [PubMed: 20123724]
85. Hu X, et al. Macrophage antigen complex-1 mediates reactive microgliosis and progressive dopaminergic neurodegeneration in the MPTP model of Parkinson's disease. *J. Immunol.* 2008; 181:7194–7204. [PubMed: 18981141]
86. Fuhrmann M, et al. Microglial Cx3cr1 knockout prevents neuron loss in a mouse model of Alzheimer's disease. *Nature Neurosci.* 2010; 13:411–413. [PubMed: 20305648]
87. Skaper SD, Debetto P, Giusti P. The P2X7 purinergic receptor: from physiology to neurological disorders. *FASEB J.* 2010; 24:337–345. [PubMed: 19812374]
88. Dinapoli VA, et al. Age exaggerates proinflammatory cytokine signaling and truncates signal transducers and activators of transcription 3 signaling following ischemic stroke in the rat. *Neuroscience*. 2010; 170:633–644. [PubMed: 20633608]
89. Lee M, et al. Depletion of GSH in glial cells induces neurotoxicity: relevance to aging and degenerative neurological diseases. *FASEB J.* 2010; 24:2533–2545. [PubMed: 20228251]
90. Carvey PM, Hendey B, Monahan AJ. The blood-brain barrier in neurodegenerative disease: a rhetorical perspective. *J. Neurochem.* 2009; 111:291–314. [PubMed: 19659460]
91. Perry VH, Nicoll JA, Holmes C. Microglia in neurodegenerative disease. *Nature Rev. Neurol.* 2010; 6:193–201. [PubMed: 20234358]
92. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci.* 2009; 32:506–516. [PubMed: 19716187]
93. Sierra A, Gottfried-Blackmore AC, McEwen BS, Bulloch K. Microglia derived from aging mice exhibit an altered inflammatory profile. *Glia*. 2007; 55:412–424. [PubMed: 17203473]
94. Endres CJ, et al. Initial evaluation of 11C-DPA-713, a novel TSPO PET ligand, in humans. *J. Nucl. Med.* 2009; 50:1276–1282. [PubMed: 19617321]
95. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. *Am. J. Epidemiol.* 2008; 167:90–95. [PubMed: 17890755]

96. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Rev. Neurosci.* 2008; 9:46–56. [PubMed: 18073775]
97. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav. Immun.* 2007; 21:153–160. [PubMed: 17088043]
98. Yirmiya R, et al. Cytokines, 'depression due to a general medical condition,' and antidepressant drugs. *Adv. Exp. Med. Biol.* 1999; 461:283–316. [PubMed: 10442179]
99. Maes M. Major depression and activation of the inflammatory response system. *Adv. Exp. Med. Biol.* 1999; 461:25–46. [PubMed: 10442165]
100. Mellor AL, Munn DH. Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? *Immunol. Today.* 1999; 20:469–473. [PubMed: 10500295]
101. O'Connor JC, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol. Psychiatry.* 2009; 14:511–522. [PubMed: 18195714]
102. O'Connor JC, et al. Induction of IDO by bacille Calmette-Guerin is responsible for development of murine depressive-like behavior. *J. Immunol.* 2009; 182:3202–3212. [PubMed: 19234218]
103. Fuchs D, et al. Decreased serum tryptophan in patients with HIV-1 infection correlates with increased serum neopterin and with neurologic/psychiatric symptoms. *J. Acquir. Immune Defic. Syndr.* 1990; 3:873–876. [PubMed: 2166783]
104. Harrison NA, et al. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol. Psychiatry.* 2009; 66:407–414. [PubMed: 19423079]
105. Piser TM. Linking the cytokine and neurocircuitry hypotheses of depression: a translational framework for discovery and development of novel anti-depressants. *Brain Behav. Immun.* 2010; 24:515–524. [PubMed: 20193757]
106. Craig AD. How do you feel — now? The anterior insula and human awareness. *Nature Rev. Neurosci.* 2009; 10:59–70. [PubMed: 19096369]
107. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Rev. Neurosci.* 2002; 3:655–666. [PubMed: 12154366]
108. James, W. *The Principles of Psychology.* Holt; New York: 1890.
109. Damasio, AR. *Descartes' Error: Emotion, Reason, and the Human Brain.* Putnam; New York: 1993.
110. Dunbar RI, Shultz S. Evolution in the social brain. *Science.* 2007; 317:1344–1347. [PubMed: 17823343]
111. Leonard WR, Robertson ML, Snodgrass JJ, Kuzawa CW. Metabolic correlates of hominid brain evolution. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* 2003; 136:5–15. [PubMed: 14527625]
112. Craig AD. Once an island, now the focus of attention. *Brain Struct. Funct.* 2010; 214:395–396. [PubMed: 20512362]
113. Picard F, Craig AD. Ecstatic epileptic seizures: a potential window on the neural basis for human self-awareness. *Epilepsy Behav.* 2009; 16:539–546. [PubMed: 19836310]
114. Asplund CL, Todd JJ, Snyder AP, Marois R. A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. *Nature Neurosci.* 2010; 13:507–512. [PubMed: 20208526]

Figure 1. Dorsal and ventral attention networks

Task-evoked activity during goal-driven attention (top left part) and stimulus-driven reorienting (bottom left part). The same networks show spontaneous correlation of activity at rest in the absence of any stimulation, response or explicit task demand (top and bottom, right part). Dorsal regions include the intraparietal sulcus (IPS), superior parietal lobule (SPL), frontal eye field (FEF) and supplementary eye field (SEF; not shown). Ventral regions include the supramarginal gyrus (SMG) and superior temporal gyrus (STG) in the temporoparietal junction (TPJ), and the inferior frontal gyrus (IFG). The region at the intersection of the inferior frontal and precentral sulcus (the inferior frontal junction (IFJ)) may function as a pivot point between the two networks^{31, 114}.