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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

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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 studies[1] led to the hypothesis that Rho GTPases

are central players in the regulation of the morphogenesis of axons and dendrites in neurons[2]. 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 journal[3] 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 morpho genesis, 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 regulate[7]. 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 disorders[8]. 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 Review[3] — 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 journal[11], 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' paper[11] was also instrumental in extending the original concept of neural synchrony from local feature binding[12] to large-scale cognitive integration[13].

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 perception[16]. 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 analysis[21]. Measuring effective neural connectivity, which involves the estimation of causal effects in neural interactions, is also generating novel insights into large-scale brain dynamics[22]. Finally, novel general frameworks for the organization of the CNS have emerged through innovative theoretical models, such as the complexity model of consciousness[23], by conceptualizing neural circuits as a `liquid state machine'[24] or by recent developments in quantitative analysis of complex networks based on graph theory[25].

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 applications[26] 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' Review[11] 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 flow[27] — 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 attention[28]. 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 Review[29] 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 Review[29] was the identification of both ventral and dorsal networks in spontaneous activity under resting conditions[32] (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 Review[29] 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 confirmed[37]. Similarly, although the phrase `reorienting' is sometimes equated with spatial reorienting, our Review[29] 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 phases[37].

An important future question is how attentional signals in frontoparietal areas modulate spontaneous activity in visual areas[38]. Answering this question will require reconciling models of attention with anatomical evidence of sparse feedforward thalamocortical connectivity[39] 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 proposed[47]. 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 messengers[49]. 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 boundaries[51]. These include the regulation of intrinsic neuronal excitability through the modulation of ion channel number and function[52] and the homeostatic regulation of synaptic strengths[51,53]. Our 2004 Review[51] 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 pro cess 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 plasticity[51]. 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 states[58] and the normalization of synaptic weights during sleep[59]. 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 mechanisms[54], 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 informatics[61]. 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 other[64].

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 strategies[67]. 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 rodents[68].

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 Review[73], 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 goals[73].

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 mPFC[73]. 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 Hyafil[77] 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 be[78].

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 Review[79] 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 activated[79]. 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 species[79]. 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 Review[79] the field has expanded exponentially. Neuron–microglia signals are now a major point of interest, with fractalkine[80,81], neuromelanin[82,83], μ-calpain[84], the macrophage 1 antigen receptor[85], CX3C chemokine receptor 1 (CX3CR1)[86] and purinergic receptors[87] 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 barrier[90] and systemic inflammation[91] 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 disease[92], 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 neurodegeneration[93]. 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 probes[94], 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 neurotoxicity[79] and disease[95], 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 published[97]. 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 acid[100]. 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 new[103]. 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 vaccination[104] 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 awareness[106]. 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 cited[107], 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 emotion[108] and the `somatic marker' hypothesis[109]. The 2009 Perspective[106] 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 hypothesis[110] and the recognition that energy utilization is a crucial arbiter of brain evolution[111].

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 Perspective[106], to the best of my knowledge, no authors had considered the possibility that consciousness might be substantialized by the insular cortex.

The 2009 Perspective[106] led immediately to the recruitment of authors for a special issue on the insula in a specialized functional anatomical journal[112], 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 Perspective[106] 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 seizures[113]. Future studies of insula function will enable deep insights into the neural basis for subjectivity, volition, individual personality and self-modulation.

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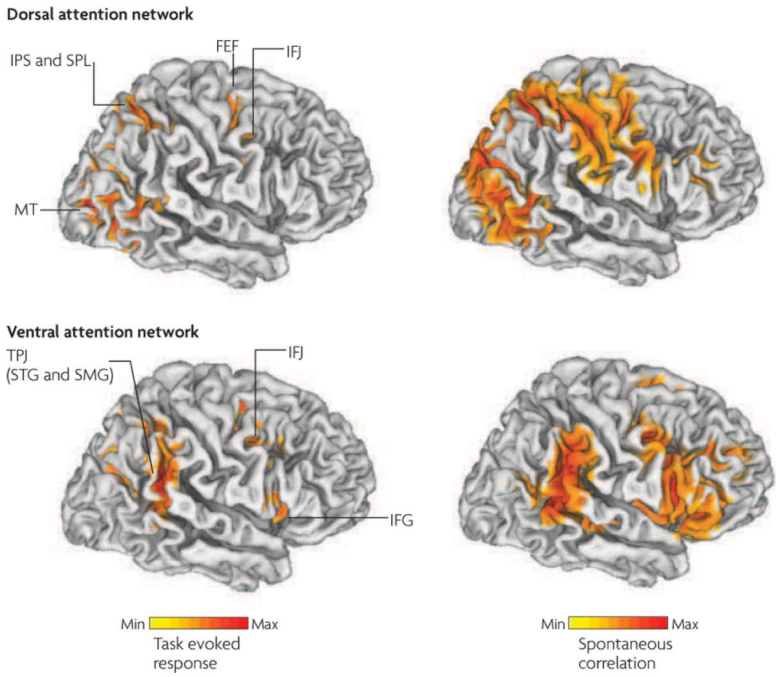

Figure 1. Dorsal and ventral attention networks

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].