Neuroscience in the 21st century: circuits, computation, and behaviour

Neuroscience has undergone radical change since *The Lancet Neurology* was launched in 2002. An explosion of new technologies has enabled discoveries that have fundamentally changed our understanding of brain function. Here, we offer our perspective on the revolution that has taken place, with a particular focus on developments in systems neuroscience. Much of this work is based on animal experiments, which offer the cellular resolution required to understand systems-level mechanisms. We start by describing the types of questions and methods that characterised neuroscience 20 years ago. We then highlight three paradigm shifts: (1) the switch from studying whole brain areas or single neurons to studying intermingled neural circuits at cellular resolution, (2) the increased focus on computation at the level of emergent properties in large neural populations, and (3) the transition from measuring neural activity in highly controlled or restricted settings to ones that accommodate ethologically relevant behaviours better (figure). Finally, we consider how this transformation will advance our future understanding of brain function in health and disease.

To understand how the brain gives rise to behaviour and cognition is perhaps the greatest goal in neuroscience. When *The Lancet Neurology* was founded, available technologies for animal experiments mostly forced investigators to address this question either by measuring behaviour or systems function after lesioning or pharmacologically silencing a specific brain area, or by recording the activity of single neurons in that area. Behaviour was typically measured under conditions quite different from those of the animal's natural environment. These approaches were (and still are) crucial in establishing potential functional roles for brain systems. Nevertheless, nowadays, most researchers recognise that explanations must be sought at the level of interactions between large numbers of heterogeneous neurons in intermingled neural circuits. To achieve a mechanistic understanding of how a system endows an animal with specific functions, researchers need to monitor the simultaneous activity of thousands of neurons in this system, and manipulate specific subsets of these, while that animal exhibits complex behaviours in a realistic setting. The tools and techniques for this approach have become available during the lifetime of *The Lancet Neurology*.

Since the mid-1900s, investigators have used ultra-thin metal wires as electrodes to monitor the activity of individual neurons while animals are exposed to sensory stimuli or exhibit simple behaviours.[1–4] Using such electrodes, neuroscientists discovered cell types whose patterns of activity correlate with specific features of a stimulus or behaviour, thus providing clues about their potential functional role. For a long time, these discoveries were most often made in sensory or motor systems. By the turn of the millenium, the scope of cortical investigations widened, with investigators searching in new areas to identify the neural basis of cognitive functions including memory, navigation,

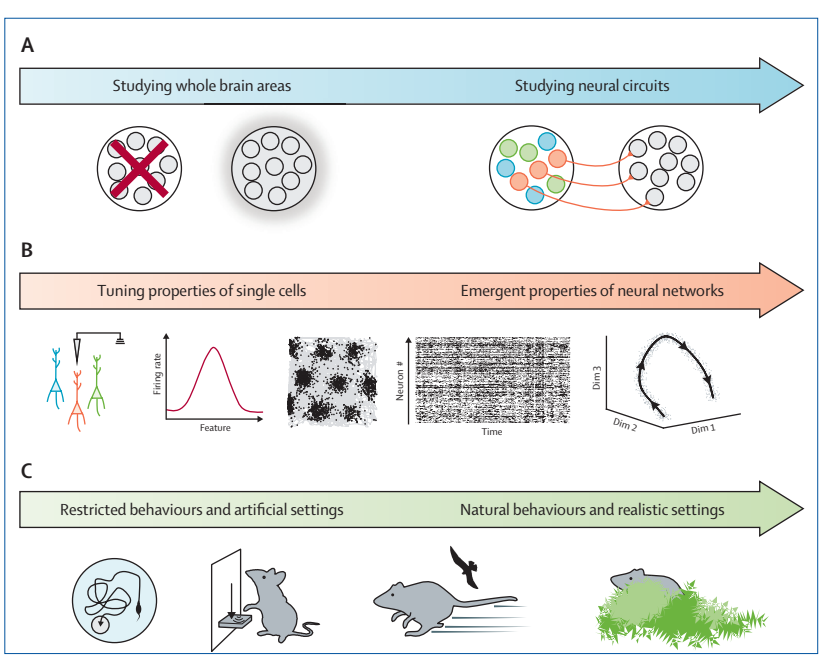

Figure: **Evolution of neuroscience during the past 20 years**
(A) In the past 20 years, neuroscience research has shifted from area-wide manipulations, such as lesions or pharmacological silencing, to circuit-level manipulations that enable researchers to target defined subsets of neurons. (B) For many decades, researchers used electrodes to monitor the extracellular activity of single neurons. The activity pattern of each neuron was often characterised by tuning curves or receptive fields. Newly developed tools can record thousands of neurons simultaneously, enabling the study of population-level dynamics using advanced computational methods. (C) Traditional laboratory experiments in artificial settings (eg, a water maze or lever-pressing tasks) often restrict animals to unnatural behaviours or stereotyped movements. Neuroscientists have moved towards studying natural behaviours (eg, prey avoidance or nesting) in more complex, realistic settings. Grid cell data and images in part B were provided by Valentin A Normand from our laboratory.

and decision making. Many new cell types with distinct tuning profiles were discovered. For example, cells in the entorhinal cortex were found to signal general features of space including distances, borders, and directions, whereas the cells they connect to in the hippocampus signal particular places.[5] Nevertheless, it became increasingly clear that understanding a particular function required the direct study of communication in neural circuits, not just their component neurons.

One barrier to studying neural circuits was the limited sample size of conventional recording techniques, which typically yielded a few dozen neurons. Breakthroughs over the past decade have overcome this barrier with both high-density silicon probes[6] and miniaturised microscopes[7,8] providing access to thousands of neurons simultaneously. However, to address the role of different circuit elements, recording more neurons is not sufficient. Dissecting circuit function requires precise intervention in specific cell types, which is now possible using molecular genetic techniques. Optogenetic[9] and chemogenetic[10] tools allow us to increase or decrease the activity of defined subsets of neurons via targeted expression of light-sensitive proteins or engineered receptors. Studies of memory traces exemplify the power of these approaches. When optogenetic proteins were expressed in the subset of neurons that were active during the encoding of a memory, subsequent stimulation of only those neurons was found to be sufficient for behavioural expression (ie, recall) of that memory.[11] Combining large-scale recordings with such manipulations can revolutionise neuroscience by revealing not only how one element in the circuit affects the others, but also how neural circuits control behaviour.

To move beyond identifying the functions of neural circuits to understanding how these functions arise, computational and theoretical approaches are crucial. Over the past century, computational models have yielded remarkable insights into a vast array of topics, including action potential generation, sensory processing, plasticity, and memory. Importantly, models generate predictions to be empirically tested. For example, early neural network models indicated that computation (eg, performing Boolean logic) often arises from distributed coding of information across a neural population,[12] rather than having single neurons act as feature detectors, as seen in sensory systems. Communication between all neurons in a circuit can lead to emergent properties with better explanatory power for behavioural and cognitive functions than single neuron responses. Such emergent properties are known to be crucial for many brain systems, but studying them experimentally is difficult. When large populations cannot be recorded simultaneously, neurons are often pooled across multiple recordings performed under nearly identical conditions. This pooling restricts the study of population dynamics to highly controlled, repeatable behaviours, and information expressed in the variability and coactivity among populations of cells is lost. Moreover, when information is distributed throughout a population, it is often inaccessible with standard techniques such as receptive field mapping and single neuron tuning curves.

These challenges have largely been overcome in the past couple of years. Simultaneously recording thousands of neurons obviates the need for stereotyped behaviour because there is sufficient statistical power to study single-trial dynamics. Information theoretic approaches[13] and novel statistical frameworks[14] can reveal the information that is encoded in a network and accommodate neurons with non-linear tuning curves. Dimensionality reduction[15] can be used to discover simpler features of population dynamics. Collectively, these approaches have become indispensable for uncovering mechanistic explanations, not just for sensory and motor functions, but also for cognitive processes such as memory and decision making. The need for synergy between computational and experimental neuroscience becomes even more urgent as neuroscientists continue to move towards brain-wide monitoring of neural activity at cellular resolution, combined with precise circuit manipulations.

If neuroscientific principles discovered in the laboratory are to be generalised to the real world, studying neural circuits during naturalistic behaviour is crucial. However, because a reductionist approach is essential for isolating specific functions, and because neural recording devices often restrict movement, the range of behaviours studied in traditional laboratory experiments has been limited and environments have been artificial. Over time, such limiting factors have funnelled neuroscience research towards highly standardised experiments in a low number of model organisms. Although ethology has had a tremendous

impact on our understanding of behaviour, its principles have been largely incompatible with contemporary neuroscientific approaches.

The emergence of miniaturised or wireless recording devices together with powerful calls for diversity of model species[16] and behaviour[17] have led to a resurgence of the study of naturalistic behaviours in the laboratory, and occasionally even in natural environments. For example, circuit computations underlying escape behaviour can be dissected in the laboratory by simulating a threat from a predator.[18] To capture detailed behavioural data, researchers can leverage the power of deep neural networks to automatically track any object or body part.[19] Studying neural circuits in natural environments is more complicated than in a laboratory environment but has been achieved during large-scale navigation in freely flying bats using wireless recordings.[20] There will always be a need for reductionism and simplicity in neuroscience, but novel tools are paving the way for ethological approaches to ensure that our understanding of brain function is not limited to artificial settings.

A mechanistic explanation of the circuit level computations underlying natural behaviour not only reveals how a healthy brain operates, but also provides insight into the dysfunction in neurological diseases and psychiatric disorders. Treatments typically act systemically and, therefore, lead to unwanted side-effects, mirroring the absence of specificity of most pharmacological interventions in animal models of the past. To diagnose brain dysfunction, clinicians need to leverage the immense body of knowledge obtained from animal experiments that reveal how specific neural circuits operate. Tools to effectively control those circuits can then be adapted for use in humans.

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