HHS Public Access
Author manuscript
Trends Cogn Sci. Author manuscript; available in PMC 2015 September 18.

Published in final edited form as:
Trends Cogn Sci. 2015 April ; 19(4): 173–175. doi:10.1016/j.tics.2015.01.007.

The unsolved problems of neuroscience

Ralph Adolphs
California Institute of Technology, Pasadena, CA, USA

Abstract

Some problems in neuroscience are nearly solved. For others, solutions are decades away. The current pace of advances in methods forces us to take stock, to ask where we are going, and what we should research next.

Keywords

future; consciousness; neuroscience methods

Introduction

My lab has a tradition of going to see science fiction movies, followed by beer and discussion of their merits. The reactions are instructive, as they partition the films into those that are a bit boring because they do not imagine enough, those that are so fantastic that they become ungrounded, and (the sweet spot) those that could possibly happen and it would be really cool if they did. Although the lines dividing these categories are fuzzy and shift with the amount of beer consumed, they reflect what we as scientists ask ourselves all the time: What should we do next? What is the most interesting question? What would you propose if somebody offered you a billion dollars? The answers, diverse as they may be, cannot simply restate facts, nor can they propose sheer fantasy. As with the movies, they need to find the most exciting place in between.

An example of this exercise comes from David Hilbert's famous 23 unsolved problems in mathematics. The Wikipedia entry for these conveniently places them into 'solved', 'proven to be unsolvable', 'ill-posed', and other categories. Although our counterpart in neuroscience cannot provide the same clean distinctions, we can certainly generate lists. As for Hilbert's problems, there is a Wikipedia entry for 'unsolved problems in neuroscience'; there are more popular writings [1]; and there are books [2,3].

In trying to brainstorm a list of my own, I read the above sources and asked around. This yields a predictable list ranging from 'how can we cure psychiatric illness?' to 'what is consciousness?' (Box 1). Asking Caltech faculty added entries about how networks function and what neural computation is. Caltech students had things figured out and got straight to the point ('how can I sleep less?', 'how can we save our species?', 'can we become immortal?'). Box 2 distills my own idiosyncratic list from all of this (admittedly biased

Corresponding author: Adolphs, R. (radolphs@caltech.edu).

towards cognitive neuroscience). Note that some future questions build on prior ones: we need to understand psychiatric illnesses before we can cure them, and whole-brain microscopic-resolution imaging of the zebrafish brain (100 000 neurons; done, although temporal resolution will improve [4]) needs to come before we do the same for the mouse brain (70 000 000 neurons), let alone the human brain (80 000 000 000 neurons).

One way of further narrowing down the questions is to mine what has been written so far in the literature to spot relationships, trends, and gaps waiting to be filled. The most straightforward case focuses on a specific region of the brain. Doing this shows that the thalamus and the insula are most in need of further study, that my favorite structure, the amygdala, is already too bloated with studies [5], and that the most popular place to look is the pre-supplementary motor cortex [6].

Rethinking methods

Another possible way forward is to focus on methods. Answers usually include words like ‘resolution’, ‘causal’, and ‘necessary’, but the question of what is the best method is actually much more treacherous than one might at first think. Does focal stimulation, no matter how specific, cause behavior? Perhaps if it is in motor structures. However, saying that stimulation of central structures causes behavior may not be saying much more than saying that stimulation of the retina causes behavior: in both cases, much or most of the rest of the brain is sandwiched in between what we manipulate and what we measure. If a lesion abolishes a behavior, does this mean the lesioned region is necessary for the behavior? Only if the rest of the brain stays the same, which it does not. Recovery of function illustrates the ubiquity of compensation, and reminds us that the brain is four dimensional. Is more microscopic always better? Not if it narrows field-of-view, which it so far always does. Even if it did not and we collected complete data about the brain [7], this might be not only unnecessary but unhelpful in guiding us towards the right kinds of models to allow further explanation. This then brings us to some ‘meta-questions’ that can help to organize the rest.

Meta-question 1: What counts as understanding the brain?

We want more than mere description, even more than prediction. So all the data in the world, by themselves, would surely not fit the bill. We need to make sense of them in some way, and the questions in Box 2 attempt to flesh out what this would entail. There is one important additional ingredient: unlike for other difficult domains of inquiry, we seem to have prior expectations about the form the answers might take. Folk psychology, our intuitive understanding of our own minds and the minds of others, places some strong (although perhaps not immutable) constraints on what could count as an adequate answer. That is why there is so little agreement, for example, on theories of consciousness – people have strong prior requirements on the answers, and what counts as an explanation for one person is missing the point for another.

Meta-question 2: How can a brain be built?

Some argue that we can only understand the brain once we know how it could be built. Both evolution and development describe temporally sequenced processes whose final expression looks very complex indeed, but the underlying generative rules may be relatively simple (for an interesting approach to discovering these rules, see [8]). Perhaps knowing how to build a brain will enable us to glean general principles that cut across the many individual questions, and across species. Or might there instead be a huge diversity of specialized and baroque mechanisms, a giant ‘bag of tricks’, that serves each organism very well for specific problems in its niche, but that share no illuminating larger themes? Probably there are both general principles as well as specific constraints and local solutions, and an engineering view would force us to map this out. There is also the hope that understanding how evolution or engineering could build a brain would help us understand what problems brains are designed to solve: what is their proper function?

Meta-question 3: What are the different ways of understanding the brain?

Here we could look to the framework proposed by David Marr [9], which asks three further types of questions. First, what is the function (of memory, of vision, of consciousness, of the brain)? Second, what are the algorithms that achieve this function (how can it be described with computational models)? And third, how is this implemented in the brain (how can neurobiologists measure it)? The implementation level reveals further levels, this time of resolution: there is implementation at the level of synapses, neurons, circuits, systems, and brains. Marr’s functional level (what he termed, somewhat confusingly, the ‘computational level’) can yield reasonable initial answers for specific systems: vision is to know what is where by looking; audition is to know what is where by listening; memory may be the ability to predict the future by learning. Harder nuts to crack are functional criteria for consciousness or cognition, and we probably have to decompose these. A further in-sight is that just as the implementation level is multi-resolution, so is the functional level. We can describe the function in terms of sensory inputs to, and behavioral outputs from, the organism. However, we could also de-scribe the function of any internal component of the brain in terms of how it transforms inputs to outputs among its immediate connections with other brain structures. It remains an open question how well this works, but some degree of such functional decomposition must be possible if we are to understand the brain at all.

Focus on algorithms

All three levels are essential, but in my view the most important may be the algorithmic. What computations describe how neural processes implement particular functions? Computations are implemented in both analog and spiking information processing that happens in structures ranging from the complex geometry of dendritic trees, to the dynamic large-scale networks that are distributed across the brain. A large range of analogies has been summoned to describe the way in which the brain computes: classical computers, dynamical systems, and the syntax of language, to name only a few. Thinking, cognition, reasoning, computation, central states, and information processing are all somehow related, but often studied from quite different approaches. All of this is important because there is reason to believe that brains compute not just in the sense that we could model their function computationally (as we could model the weather), but in the sense that this may be the proper function of nervous systems. (Which is not to say that computation is a function unique to nervous systems).

Concluding remarks

In a nutshell, then, the biggest unsolved problem is how the brain generates the mind, conceived of in a way that does not simultaneously require answering the problem of consciousness (Box 1). We can perfectly well ask about cognition and computation without asking about subjective experience – although one would hope that a full understanding of the first two might eventually explain the third. Indeed, a mark of success in understanding how brains compute should be that this would provide us with answers to all the related questions (what is cognition? what is psychology?). This is of course a very tall order. The only plausible approach, in my view, is to make comparisons, across species and across levels. We cannot understand how we reason and think until we understand cognition broadly across species; and we cannot understand that unless we understand relations between all the levels that describe what a brain does. Nobody said this would be easy.

References

1. Eagleman D. 10 unsolved mysteries of the brain. Discov. Mag. 2007 Aug. 2007.
2. van Hemmen, JL.; Sejnowski, TJ. 23 Problems in Systems Neuroscience. Oxford University Press; 2006.
3. Markus, G.; Freeman, J. The Future of the Brain. Princeton University Press; 2015.
4. Ahrens MB, et al. Whole-brain functional imaging at cellular resolution using light-sheet microscopy. Nat. Methods. 2013; 10:413–420. [PubMed: 23524393]
5. Beam E, et al. Mapping the semantic structure of cognitive neuroscience. J. Cogn. Neurosci. 2014; 26:1949–1965. [PubMed: 24666126]
6. Behrens TEJ, et al. What is the most interesting part of the brain? Trends Cogn. Sci. 2013; 17:2–4. [PubMed: 23218941]
7. Koch, C.; Marcus, G. Neuroscience in 2064: a look at the last century. In: Marcus, G.; Freeman, J., editors. The Future of the Brain. Princeton University Press; 2015. p. 255-269.
8. Menezes T, Roth C. Symbolic regression of generative network models. Sci. Rep. 2014; 4 Published online September 5, 2014. http://dx.doi.org/10.1038/srep06284.
9. Marr, D. Vision: A Computational Investigation into the Human Representation and Processing of Visual Information. W.H. Freeman and Co; 1982.
10. Block, N. Consciousness, big science, and conceptual clarity. In: Marcus, G.; Freeman, J., editors. The Future of the Brain. Princeton University Press; 2015. p. 161-176.
11. Chalmers D. Facing up to the problem of consciousness. J. Conscious. Stud. 1995; 2:200–2019.
12. Naci L, et al. A common neural code for similar conscious experiences in different individuals. Proc. Natl. Acad. SciU.SA. 2014; 111:14277–14282.
13. Mantini D, et al. Interspecies activity correlations reveal functional correspondence between monkey and human brain areas. Nat. Methods. 2012; 9:277–282. [PubMed: 22306809]

Box 1

Consciousness, easy and hard

A perennial entry on any list of unanswered questions, consciousness fractionates into multiple problems. Some have seen so much advance that they fall into the 'solved/soon solved' category: the psychophysics of conscious experiences, and aspects of what neurological factors globally distinguish the state of being conscious from being unconscious. Then there are two 'hard' questions of consciousness, one methodological and the other conceptual. Methodologically, it is very hard to see how the neural correlates of a conscious experience can be separated from everything that accompanies such a conscious experience (our own access to it required for reporting it, antecedent events that make the experience possible, and other events that blur into constitutive components of consciousness) [10]. Conceptually, it remains hard for us to understand why neuronal events, even if we were able uniquely to isolate them, should give rise to a particular conscious experience, or indeed to any conscious experience at all [11]. These difficulties notwithstanding, there are intriguing suggestions that we could at least compare the neural correlates of experiences among different people and thus begin to map out individual similarities and differences [12], perhaps even extending this to comparisons with nonhuman primates [13].

Box 2

The unsolved problems of neuroscience

Problems that are solved, or soon will be:

I	How do single neurons compute?
II	What is the connectome of a small nervous system, like that of *Caenorhabitis elegans* (300 neurons)?
III	How can we image a live brain of 100 000 neurons at cellular and millisecond resolution?
IV	How does sensory transduction work?

Problems that we should be able to solve in the next 50 years:

V	How do circuits of neurons compute?
VI	What is the complete connectome of the mouse brain (70 000 000 neurons)?
VII	How can we image a live mouse brain at cellular and millisecond resolution?
VIII	What causes psychiatric and neurological illness?
IX	How do learning and memory work?
X	Why do we sleep and dream?
XI	How do we make decisions?
XII	How does the brain represent abstract ideas?

Problems that we should be able to solve, but who knows when:

XIII	How does the mouse brain compute?
XIV	What is the complete connectome of the human brain (80 000 000 000 neurons)?
XV	How can we image a live human brain at cellular and millisecond resolution?
XVI	How could we cure psychiatric and neurological diseases?
XVII	How could we make everybody's brain function best?

Problems we may never solve:

XVIII	How does the human brain compute?
XIX	How can cognition be so flexible and generative?
XX	How and why does conscious experience arise?

Meta-questions:

XXI	What counts as an explanation of how the brain works? (and which disciplines would be needed to provide it?)

XXII How could we build a brain? (how do evolution and development do it?)

XXIII What are the different ways of understanding the brain? (what is function, algorithm, implementation?)