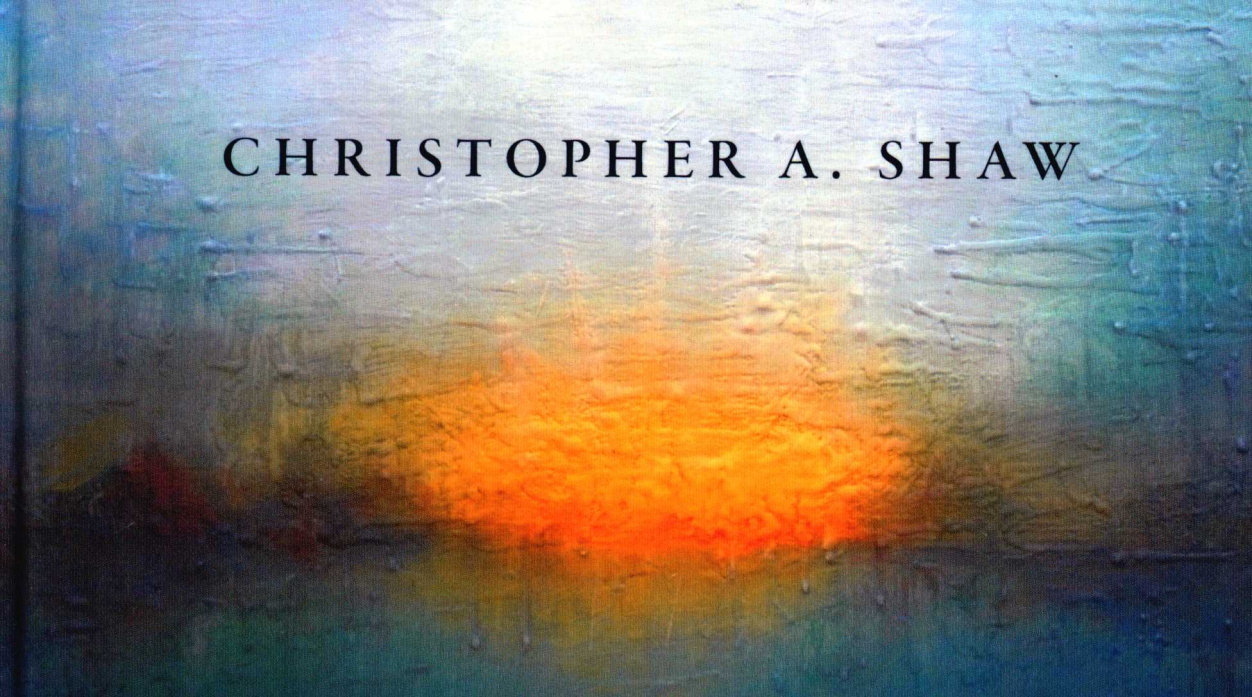
CHRISTOPHER A. SHAW



NEURAL DYNAMICS OF NEUROLOGICAL DISEASE

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Neural Dynamics of Neurological Disease

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Preface

"Babylon in all its desolation is a sight not so awful as that of the human mind in ruins."

Scrope Berdmore Davies[1]

"I can face death, but I cannot face watching myself disappear from within…I don't know who I am anymore."

Claude Jutra[2]

Each annual meeting of the Society for Neuroscience (SfN) is, for me, once more a reminder just how reductionist the field of neuroscience has been, continues to be, and apparently is destined to remain.

Anyone who has gone to this conference, or any similar type of large meeting, cannot help but be overwhelmed by the sheer quantity of the information on display. During the three and a half days of the main SfN meeting, some 30 000 participants will present over 15 000 posters along with almost 13 000 talks of various lengths. These numbers were the projected figures for the 2014 conference in Washington, DC, but other SfN conferences of the recent past will have been much the same in size. Future conferences will likely be even larger.

Most of the talks at the meeting occur in the so-called "mini"- and "nano"-symposia which feature 15-minute-long presentations, each usually containing a small body of data and its preliminary interpretation. However, the poster sessions really show the true dimensions of the conference: seven 4-hour-long sessions, each filling an area the size of several football fields.

Each poster, or mini-talk, contains a snippet of information – almost all of it, as noted, preliminary – a lot of which will turn out to be conceptually flawed in design or experimentally incorrect. Much of the time, as the lack of later publications bears out, the work is simply not reproducible. This outcome is in accord with studies by various scholars who have noted a lack of reproducibility in experimental data of all kinds, perhaps particularly often in the biomedical sciences.

Multiply these numbers by the additional numbers of people and presentations at conferences in neurology or more specialist neurological diseases, multiply again by the number of years these conferences have all been going on, and one likely gets billions of words and millions of tons of paper in a virtual tidal wave of information, which, combined with endless time spent by a great variety of otherwise quite talented scientists,

actually produces what, at the end of the day, amounts to relatively little useful information about neurological diseases. Further, very little of this information is actually sorted, compiled, or cross-checked internally or externally with the previous decades of results from all of the similar meetings.

What then are the outcomes for neurological disease remediation? First, the field still does not understand the etiology of most neurological diseases, and, as a consequence, it has only a very limited means of translating what it thinks it knows into treatments that actually halt the progression of – never mind "cure" – these diseases.

The problem here is therefore obviously not one of quantity, or even in many cases of quality. Rather, the problem is that the field still cannot answer some really fundamental questions about the diseases in question and therefore cannot come up with treatments that make a lot of sense mechanistically or, at the very least, do what they are intended to do. Maybe what this really means is that the field of neurological disease research is not asking the right questions, or that it does not know how to interpret the answers.

For me, the question is not how to (over) simplify the nervous system and its diseases, but rather how to understand them in their entirety. Admittedly, the task of understanding the former has proven quite difficult. The second goal clearly depends on accomplishing the first.

As other authors have pointed out in different contexts, attempts to "atomitize" a subject of study into ever smaller bits without any context to their inter-relationships can be enormously detrimental (see, for example, Gould and Lewontin, 1979). Further, should the field really expect that a system as complex as the nervous system will break down in a simple way, or should it expect that its pieces will, in some measure, reflect its overall innate complexity? Almost for sure, it is the latter. At least, this is the perspective I will take in the pages that follow. I should acknowledge here that my bias against overusing reductionist approaches when considering neurological disease origins in as complex a system as the human central nervous system (CNS) is very much the polar opposite to the tack taken by Dr. Christof Koch, one of the foremost theorists on human consciousness (see Koch, 2012). The latter subject is surely as complex as the breakdown of the CNS in neurological diseases, but there may be some common ground (see Chapter 14).

As will be discussed in this book, the origin, function, and diseases of the nervous system are, by their very nature, complex, and are highly interconnected amongst the various types of cells and regions affected. The concept of biosemiosis, or biological signaling, is in this context highly relevant, and it will be highlighted in much of the discussion that follows. Moreover, the diseases upon which this book will focus are "progressive," meaning that they continue to get worse in terms of nervous system pathology and functioning over time. They are also age-related and somewhat sex-dependent, are complicated by the added complexities of genetic variations, individual microbiomes, and a host of other likely contributing factors.

How all of these aspects combine to produce any neurological disease is actually something that neurological disease research has not really begun to understand. If the nervous system is constructed as a complex system both developmentally and functionally, which it decidedly is, then it is surely so when it malfunctions. In brief, those of us in what can broadly be described as the neurological disease "field," a term that will be used throughout the book, are in rather dire need of a conceptual frame shift.

Many scientists are hard at work to accomplish such a shift, but they are swimming against a powerful tide of overwhelming amounts of data, which, as noted earlier, are

often incorrect. How, then, is one to sort the wheat from the chaff, the valid from the invalid?

This book is intended to help the process along. Inevitably, in so doing, it will annoy some of my neuroscience colleagues as it may seem to imply that all their myriad experiments – often with amazingly spectacular methodologies – are not going to get the field to any answers without reframing the questions. Techniques are, after all, merely the equivalent of tactics in a military setting, simply, in this case, the means to accomplish the larger strategic goal of understanding these diseases. The strategic goal is aimed at an end state of prevention (or of effective treatment, as the second-best option).

Understanding this end state is actually critical to our collective wellbeing, because these various diseases are threatening to overwhelm the medical systems of the developed nations. (As for the developing countries, their medical systems are in many cases in poor enough shape as is, and hardly need the added burden of increased neurological diseases.)

My hope is that *Neural Dynamics of Neurological Disease* will spark debate. Time will tell if this hope has been realized. While desirable, indeed essential, from my perspective, such an outcome is decidedly a long shot. Scientific journals and meetings such as the SfN have become major industries, and are often mired in dogma, with an apparently dominant philosophy that "more equates to better."

It is clear from the work of Prof. John Ioannidis and others that more is not necessarily better if the data are incorrect or interpreted incorrectly and/or are not verified by replication, or at least convergent forms of information. Thus, of the approximately 28 000 talks and poster presentations at SfN, some two-thirds (or more) will be incorrect, and virtually none will be replicated. This is a vastly larger problem than most of those in the field realize, and I will touch upon it further in Chapter 8.

It is reasonable to assume that much of what follows in this book will be controversial, not so much because the data are contested (although in many cases they are) but because the way I have chosen to put them together in particular categories leads to certain conclusions. Other authors, ordering the subjects in different ways, might reach very different outcomes. In this sense, the process of writing a book is a lot like museum curatorship in that what one chooses to put on display versus what one leaves in the basement will provide very different narratives. When writing about neurological diseases, how one collates and arranges the key subjects and lesser items shapes the presentation, and thus the conclusions. And, needless to say, all authors have their own assumptions, prejudices for or against certain hypotheses and data, and ways of viewing any particular field of study.

Given this, it seems only fair at the outset for me to state my own assumptions. These are listed in a sequence from what I hope will be the least controversial, "motherhood" sorts of assertions to those that perhaps deviate to a lesser or greater extent from mainstream concepts of the nervous system in disease. Each will be bolstered by the relevant literature in the appropriate places in the book's chapters.

One point to be addressed first, however, is the following: the terms "disease" and "disorder" tend to be used synonymously when speaking of those conditions that afflict the human nervous system. This consideration applies particularly to those diseases that are the main focus of this book, namely Parkinson's disease, amyotrophic lateral sclerosis (ALS) (colloquially called Lou Gerhig's disease, although it might just as well have been termed Charcot's disease, as it sometimes has been), and Alzheimer's disease. Is it correct to term these conditions "diseases"? The difference between the two words can be

subtle. "Disease" is normally used in the sense of sickness or illness. These neurological conditions fit this definition, and hence their names are appropriate. In addition, there is some evidence – not particularly strong, but evidence nevertheless – that they actually arise as part of an infectious process. Hence, calling them "diseases" is even more correct. In regard to the word "disorder," various dictionaries define it to mean "an illness that disrupts normal physical or mental functions." These conditions definitely do both, so it is equally correct to refer to them as "disorders." Therefore, with apologies to the purists amongst the readers, the terms "neurological disease" and "neurological disorder" will be used interchangeably in the chapters that follow. When speaking of specific conditions (e.g., Alzheimer's disease), the word "disease" will always be used.

With that out of the way, I want to introduce the central theses to be addressed, not necessarily in the following order:

1) The human CNS is complex. It contains something on the order of 86 billion neurons, organized into multiple subsystems, surrounded by 85 billion supporting glial cells. Neurons are totally dependent on these support cells for their normal functions. Each neuron connects to multiple other neurons for an estimated 94 trillion synaptic connections. There should be nothing particularly controversial about anything in this paragraph for anyone in neuroscience/neurological disease research.
2) The complexity of the nervous system arises due to the interplay between genetic programs and environmental influences. This complexity includes the interactions that lead to neurodegeneration. Gene defects in the germ cell line and in the early developing CNS are likely to be fatal or result in profoundly disturbed neuronal functions. Environmental impacts on the CNS depend crucially on the stage of development: prenatal ones are likely to be of greater impact than those occurring in postnatal life, while early postnatal ones will be more impactful than those later in life. The concept of the "fetal basis of adult disease" used in other fields of study likely applies to neurological disease just as strongly (or even more so) to those disorders with which it is more conventionally associated. Environmental impacts also crucially depend on the number of CNS levels impacted (e.g., from genome to the whole CNS).
3) It is almost certain that gene defects/mutations alone will not explain most types of age-related neurological disease. Nor, for that matter, will obvious environmental stressors/toxins be found to be solely responsible in most cases. Hence, gene–toxin interactions are the likely source of most such diseases, acted upon by a number of other variables across the lifespan.
4) Neuronal compensation for genetic or environmental insults to the CNS will be limited by the type of insult and the stage(s) at which they occurs. Early gene defects, if not rapidly fatal, may be compensated for by redundancy of function of other genes. Environmental impacts, if they do not cross too many levels of organization, may allow for neuronal compensation by unaffected cells or regions. "Neuronal plasticity" is not a simple process, nor one strictly limited to the stage of neuronal development.
5) For all of these reasons, neurological diseases that are age-related (e.g., Parkinson's disease, ALS, Alzheimer's disease, and others) are going to be complex as well. The same applies to neuronal disorders at the other end of the age spectrum (e.g., autism spectrum disorder (ASD)).

6) At least for Parkinson's disease, ALS, Alzheimer's disease, there is only one, possibly two, real neurological clusters with a sufficient number of afflicted patients to allow effective epidemiology. The first cluster is ALS–parkinsonism dementia complex (ALS-PDC) of the Western Pacific. This includes the islands of Guam and Rota (where it was first described), Irian Jaya, and perhaps the Kii Peninsula of Japan (whether the CNS disorders in Kii are related to the others is an area of some controversy). The second possible cluster is the form of parkinsonism associated with consumption of the soursop fruit on the French Caribbean island of Guadeloupe.
7) The gene–toxin interactions leading to neurological diseases are not CNS-specific, but impact other organ systems as well. They may not be the cause of death or nervous system dysfunction, but ignoring these other organ impacts misses a number of crucial clues to disease etiology.
8) Still other organ systems are likely significantly involved in neurological diseases. A good example is the immune system in which autoimmune reactions may be a primary player in the onset and progression of some neurological diseases. The immune system also plays important roles in normal neuronal development.
9) Because of the complexity and interconnectedness of the CNS, damage at any level must necessarily cascade to other levels (e.g., cell to circuit, circuit to a particular region, etc.). So-called "cascading failures" will, at some point, trigger a total system collapse. Thus, after such a critical stage is reached, no effective therapy will be possible. For this reason, therapies designed to target late stages of disease, namely most at the "clinical" diagnosis stage, will inevitably fail and may simply exacerbate rather than relieve underlying pathological processes. The concepts from biosemiosis of the "true narrative representation" (TNR) apply here.
10) Any models of neurological diseases, no matter what kind of model or for which disease, are at best a limited means of understanding the complexity of the particular disease. They are even less effective in developing therapeutic approaches to early or late disease states.
11) Many of the data in the literature in any of the subfields of neurological disease research are likely to be wrong and thus highly misleading. Each subfield needs a thorough review to cull such incorrect material. This is not likely to happen.
12) Each of the sporadic/gene-susceptibility age-dependent neurological diseases represents not one entity but a spectrum of related disease states. Each case is therefore individual. Against such individual (and thus, unique) presentations, there can never be a generalized treatment. This applies particularly if treatment options are begun post-diagnosis. Effective treatments for neurological diseases, if they occur at all, can arise only from prophylaxis or the next-best option of extremely early-phase detection followed by strategic, targeted therapy. The only way to get to this stage is for governments and other entities to commit significant funds to providing a new perspective on such diseases. Essentially, this is a policy discussion, in which social priorities need to be carefully examined. Policy considerations are not the traditional role of scientists, but without the input of those doing the research, a policy re-evaluation will almost certainly not happen. Whether it does or does not is a choice. Needless to say, choices have consequences.

These last comments are really the focus of this book, and were fleshed out from some very preliminary thoughts as I walked the Camino Frances of the Camino de Santiago. For those who do not know it, the Camino actually describes a number of routes, mostly

in Spain and France, which all end up in the Galician city of Santiago de Compostella. Even on a single route, although the conventional end point remains the same, the geography can vary from year to year, as a result of human activity and weather. How one actually walks the Camino varies with season, personal fitness, past or acquired injuries, frame of mind, companions, and so on. Not everyone finishes. For those who do complete the Camino, no two journeys are the same. Thus, one often hears the expression, "walking one's own Camino."

All of this leads to the point hinted at earlier: no two neurological disease manifestations, even in ostensibly the same disease, are actually the same, except perhaps at disease end state. Everyone walks their own Camino of neurological health. This metaphor, I think, has significant implications for neurological disease detection and treatment.

Four final points – caveats, really – need to be acknowledged, all of which will be discernible to readers in due course. First, just as neurological diseases are not linear in how they develop, progress, or complete, this book is not linear either. While there is a trajectory that leads from the first pages to the final conclusions, the book could not be written as if it were a simple story. Rather, it is recursive in fact and concept, with various themes being introduced and then reconsidered pages later as new information is added. Some readers may find that this makes parts of the book redundant. I hope, however, that such readers will see that any one such theme is expanded by the stage of the book and the discussions that have occurred since it was last raised.

Second, in some sections I describe the work of my laboratory and colleagues in more detail than I do the work of others. The reason is simple: I know my own work best – the valid parts as well as the invalid. I hope I have not done such self-selection too blatantly, or too often.

Third, in areas that are likely to prove particularly controversial, I err on the side of providing too many, rather than too few, primary literature references. This point ties in with the fourth caveat: The book is written mostly for my fellow neuroscientists and for those in the neurological disease world. This focus inevitably leads to some pretty dense – and reference-filled – expositions, which may be daunting for any nonspecialist scientists or the lay public. A glossary is provided at the end, which I hope will help.

That about sums it up.

Needless to say, in all of the following material, any errors in citation, content, or interpretation are purely my own.

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Endnotes

1 Scope Berdmore Davies (1782–1852) was a dandy and friend of Lord Byron.
2 Claude Jutra (1930–1986) was a Quebecois director, screenwriter, film editor, cinematographer, and actor. After being diagnosed with Alzheimer's and living with the condition for a time, Jutra committed suicide. In recent years, his reputation has been stained by allegations of pedophilia.

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In this last year, as the book took shape in the various intellectual and geographically peripatetic ways in which it was written (Paris, Vancouver, Los Angeles, the Camino de Santiago, Lucy sur Yonne, and Victoria), my son Caius was born and my mother, Peggy O'Shea, and my father, Lou Shaw, died. This book is therefore dedicated to the future of my son and the memory of my parents. *Buen Camino* to my son as he travels through life and to my parents for lives well lived and long journeys well taken.

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