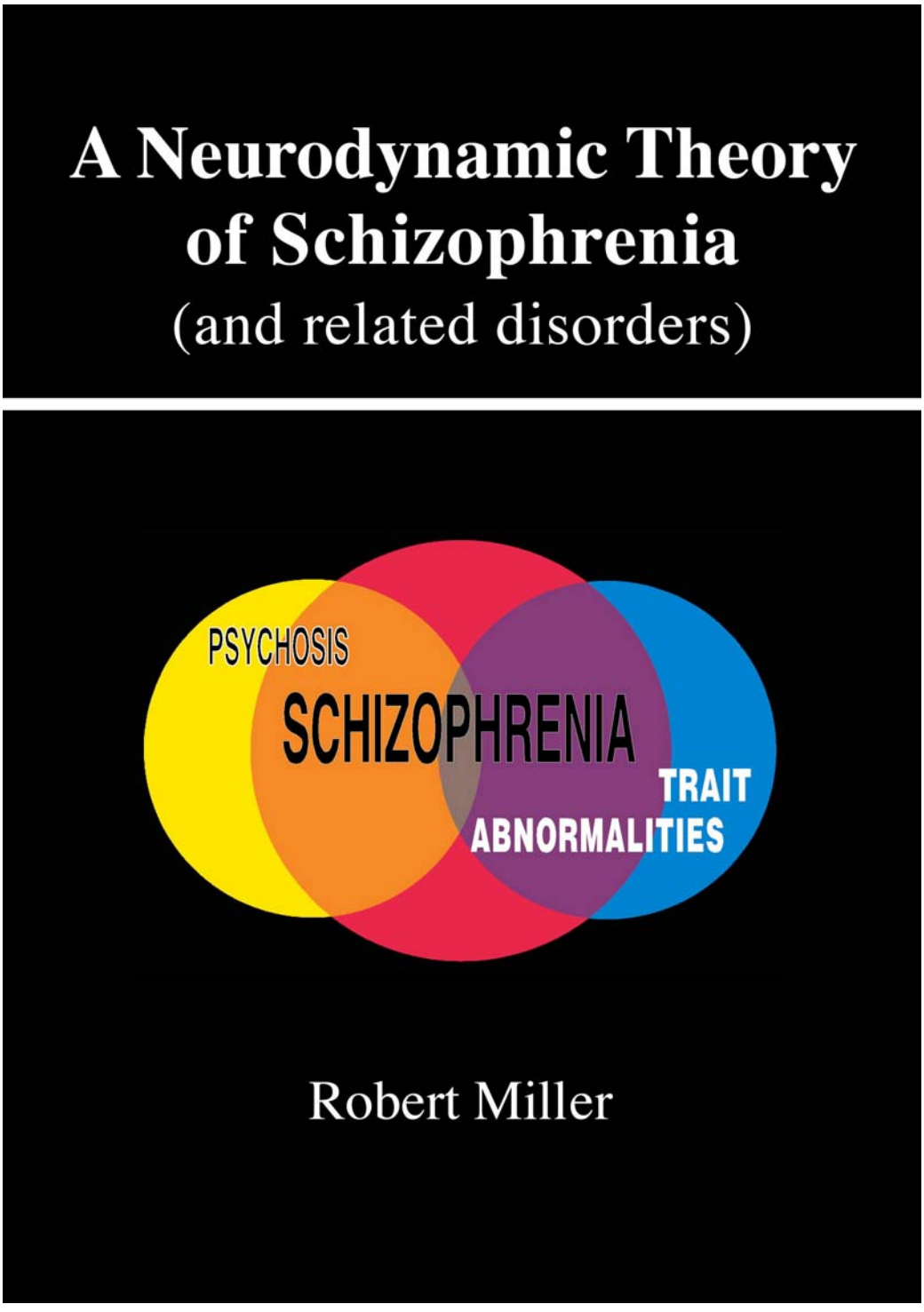
“A Neurodynamic Theory of Schizophrenia”: Introduction.

Lecture delivered at “Winter Workshop on Schizophrenia and Bipolar Disorders: Montreux 5th February 2008.”



I did speak once before at one of the Winter Workshops, in the early 1990s. It was a rather stressful occasion, for reasons which I won't go into; and it is easier for me now, because my objectives in this area of research are now largely fulfilled. It is easier on this occasion also, because I am flying my true colours - that is as a researcher, who is also an ex-patient. At the international conferences on HIV/AIDS, which I believe are larger than this one, I understand that the people who are personally affected by HIV/AIDS play a big part - perhaps even a pivotal part -in the proceedings of those conferences. It is high time that there was also such consumer participation at the Winter Workshops - and there is an increasing number of people who could play such an important role - informing you, so to speak, of the view "from the other side of the mirror". When I use that metaphor, of course it should be clear that it is you who are the reflection, not me.

I have four objectives in this talk: *First* I want to give a brief account of my own story, and how I got involved in schizophrenia research. *Second*, again briefly, I want to make some general comments, somewhat political in nature, about research on schizophrenia, and the research environment in which many of us now operate. I hope you will bear with me; but I think these points do need to be made explicitly, forcefully, and in a public forum. *Third*, the main part of my talk, will be to explain some of the key parts of the theory I have recently completed. Now, as symbolized in my illustration, I believe we need two nearly separate bodies of theory to account for schizophrenia, one for dopamine-mediated psychosis, the other for the underlying constitution or diathesis. My ideas on the first have been developing over the last 30 years, and are already published, so I won't spend much time on that. However, my ideas on the underlying diathesis for schizophrenia will be new to you, so I want to spend more time on them. Lastly, I want to leave plenty of time for a wide-ranging discussion, because, in the audience, there are undoubtedly people with expertise in specific areas of this complex field far beyond my own.

So, first, my own story: I started as a medical student at Oxford in the early 1960s, and even in my first year, was very interested in the workings of the brain. However, I was also suffering increasingly severe psychiatric problems, which at that stage consisted of dramatic fluctuations of mood. At Oxford, medical students generally obtained a first degree, before going on to the clinical part of their training, and I did manage to get a BA in physiology, and did one year of research in single unit neurophysiology, despite these quite disabling problems. However, after that, as a clinical student at one of the London teaching hospitals, I was totally overwhelmed

by a sudden and catastrophic psychotic breakdown. So I experienced at first hand what coercive admission to a mental hospital was like, and in the immediate aftermath, I made a quite serious suicide attempt. I was put on antipsychotic drugs, and was in hospital for six months. I have been on those medications ever since, and they were undoubtedly a life-saver. However, in the first few years, I should say that the dose I was prescribed was many times too large; and it was only my own assiduous and rather risky experimentation which eventually worked out the correct small dose. Prior to that, I lost two or three years of active life because I was so heavily sedated. Of course any attempt to finish the medical course was abandoned; but, a few years later, I got a job at Glasgow University in Scotland, was able to work for a Ph.D., and eventually graduated in 1973.

In that year, within a few months, three very important things happened. I first heard mention of the transmitter dopamine in the context of schizophrenia - actually from my Ph.D. examiner Leslie Iversen, who spoke at the workshop two years ago. I should say that my own thesis was on another neurotransmitter - glutamate - and in invertebrates. That chance remark of Iversen started off one of the themes of my subsequent research. Second, as a post-doctoral student, now back in Oxford, I did experiments which have proved to be critical for the theories of schizophrenia I have been developing in the last 15 years. More on that in a moment.

But most important, I thought it was the right time to do the critical test of whether I still needed to take those medications, even in small doses - so I tailed them off over a period of a couple of months, had a fine climbing holiday at Zermatt, and then, when fit, relaxed, and with no stress on the horizon, I stopped them completely. Well, within a few weeks, I became floridly psychotic, and was in hospital again, but this time only for a short period. This was far less traumatic than the first time in hospital, though a truly colossal experience. I knew I would come right once the medications started to work - and in the course of this I learned *so much* about the actual psychology of florid psychosis; and this has been a source of insight upon which I still draw. In particular I was struck by the fact that the medications take weeks or months to produce their full benefit, although the dopamine receptors are presumably blocked within a few hours. I should also say that I now realize that such immediate relapse on stopping medication is not the most typical pattern. We could discuss that later.

Anyway, in the aftermath of that episode, I realized that I had an excellent education in the neuroscience of the time, a very clear memory of my periods of illness, and my wits were -surprisingly - still mainly intact; so I made the decision that, if possible, I wanted to devote my research efforts

towards understanding schizophrenia and related disorders. (I did receive a number of different diagnoses, but the only one which was offered by someone who had actually seen me when I was ill was in fact schizophrenia.)

I had difficulty getting a secure job in Britain, so in 1977 I emigrated to New Zealand, to a job in the Anatomy Department at Otago University. It gradually became clear to me that I was not very good as an experimental scientist, so the strategy of research I gradually evolved was what I call "library-based theoretical research". That involves studying many thousands of papers, and piecing together the complex jigsaw puzzles about normal brain function, and its abnormality in major mental disorders. The year I arrived in New Zealand, the Schizophrenia Fellowship was founded - I pay tribute to the enormous courage of the people who founded that organization - and I have worked with them ever since. I had no medical qualification of course, let alone a psychiatric qualification, but it was through my contacts there that I was able deepen my understanding of this complex disorder.

To cut a long story short, the period 1980-1995 was spent working on the theory of psychosis - the sort of severe mental turmoil I had experienced earlier. This of course drew heavily on my understanding of that messenger substance, dopamine. By the 1990s, I had however realized, as people had been telling me for years, that there is more to schizophrenia than episodes of psychosis. There is a long list of non-psychotic abnormal traits, present even in well-stabilized patients. I've been working on that topic in the last 15 years. More on that in a moment.

Now let me go on to the somewhat political bit. Although I still take medication, and the memory of my periods of illness is still green, that was all a long time ago, and I am now a very different person. I have no intention here of going on a grievance trip about the inadequacies of mental health services as I experienced them. This is a research meeting, and I want to look to the future, not the past. However, I *do* want to challenge you - challenge, perhaps even provoke; but if you think I am being provocative, I assure you, I too have been provoked.

Last year, at the International Congress on Schizophrenia Research at Colorado Springs, there was a debate on whether the name "schizophrenia" should survive into DSMV, and if not, what it should be replaced by. Robin Murray suggested that the word "schizophrenia" should be abandoned, and eventually replaced by "dopamine dysregulation disorder". I certainly agree that any new name should be based on a known cause; but, as Will Carpenter and others pointed out - and I strongly agree - there is far more to

schizophrenia than dopamine-mediated psychosis. However, Will confessed that he hadn't the foggiest notion of what the fundamental cause might be - so we should wait awhile before we come up with a new name.

But to my mind, that confession of Will represents a great failure - on a large scale - of the whole of the international research community studying this disorder. So, in the next few minutes, I want to analyse the nature of that failure. To do that, let's step back from psychiatry, for a moment, and consider it in the overall context of that enterprise called "science". The critical step which brought science into existence in the seventeenth century, with pioneers such as Galileo and Newton, was that for the first time - with the possible exception of Archimedes and some of the Arabic scientists - sophisticated theoretical reasoning was combined with systematic empirical observation. That combination - of well-reasoned theories with experiments - is at the heart of science. Very often, this results in what can be called *"cross-level explanations"* - of phenomena at a high level in terms of data or hypotheses at a lower level. I say "hypotheses" because, very often - for instance in the case of Dalton's atomic hypothesis, or Gregor Mendel's hypothetical genetic factors - the techniques were not available to verify directly the critical assumptions; so support for those assumptions was indirect, based mainly on what they would explain at the higher level. There are many examples of this pattern in physics, some in biology, *but none in psychiatry*. So, psychiatric research piles up mountains of data, with no real attempt to understand what they mean. Sophisticated reasoning *is* used for design of experiments, and for statistical analysis, but there is no attempt at the coordinated *causal* reasoning, needed to establish true disease theories.

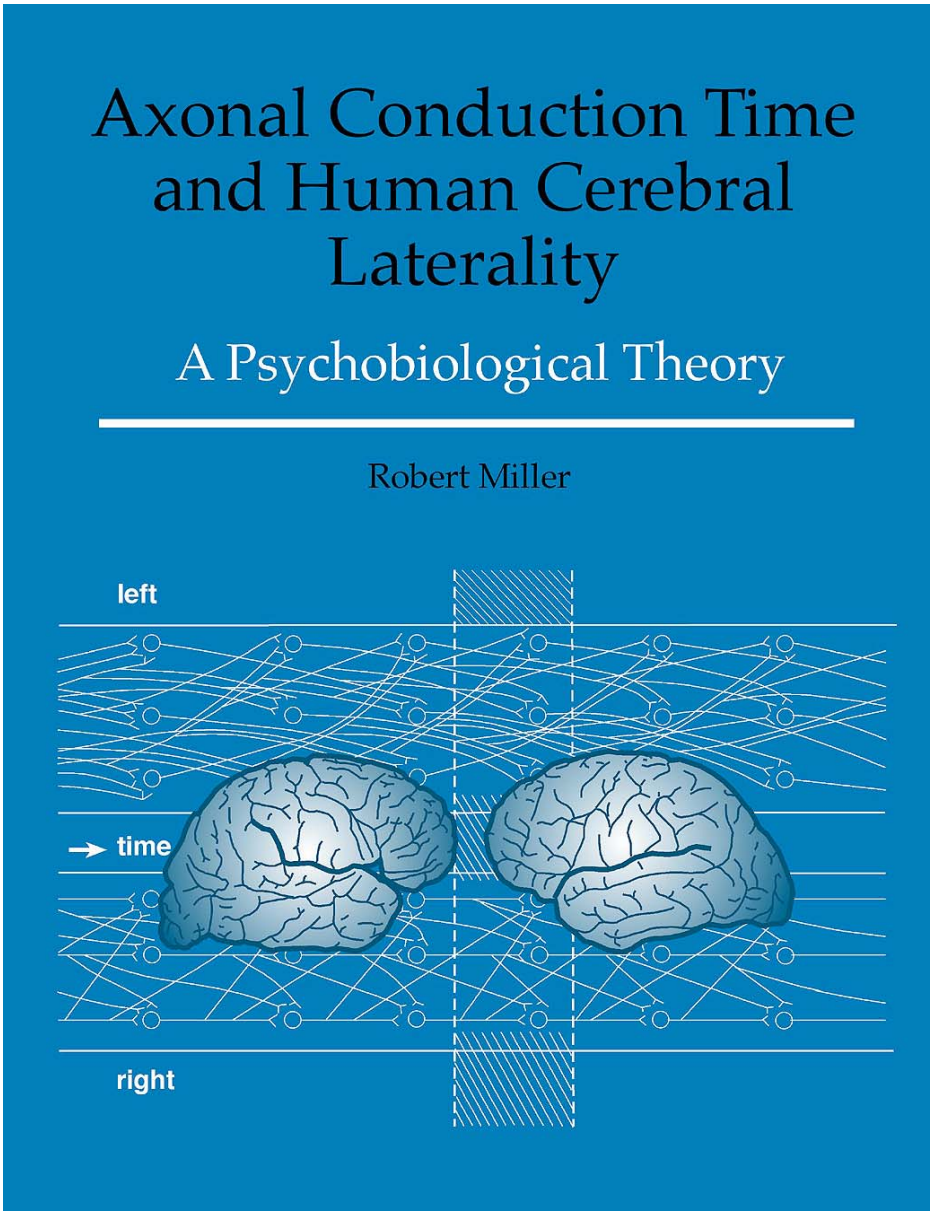
Here I should make the point that, although I tend to take theoretical physics as my paradigm, I do not think that the coordinated reasoning needed to understand major mental disorders would have such a strong basis in mathematical arguments. Instead, what I think is required is painstaking, meticulous scholarship on a very large scale, combined with imaginative reconstruction of what might be going on in causal terms, and then - quite essential - the development of explicit, testable predictions.

Why has psychiatry failed to take theory seriously? Many reasons could be suggested, but I will focus on three.

The *first* may be a general characteristic of medical compared with science education. The primary experience in medical education is the encounter, one-on-one between doctor and patient, totally uncontrolled in any scientific sense. So physicians tend to be very sceptical of any attempt to explain anything based on such encounters. That's exactly as it should be; medicine at that level is more of an art than a science. In addition, in medical

education, would-be physicians are rarely exposed to examples of true cross-level explanations, as a student in physics would be. Instead there are many references to risk-factors and other correlations. Unfortunately, when such physicians become researchers, the same habits of mind stick with them, and they carry over into the research field the same scepticism or ignorance of true explanations. Induction, based on clinical experience prevails. Deduction, based on understanding mechanisms is suspect. Indirect inference about what might be going on is second class. The archetype of this rigid empiricism is the apostle St. Thomas, who, you may remember, was a physician, and actually wanted to feel the holes in Christ's hands. Nothing less direct would suffice.

However, in biological psychiatry, the situation is worse than in most medical research, so the characteristics of medical education can't be the whole of the answer to my question. I recently had a conversation with one of the prominent schizophrenia researchers in Australia - he's not here, and I won't name him - and he made the point that we can't hope to get real cross-level explanations of mental disorder in terms of neuronal dynamics, because we don't understand how the normal brain works. Well, he's not a real neuroscientist, and he's not up with the play. In fact, as soon as I become seriously involved with schizophrenia research, around the year 1980, I had realized his point, and so much of my work since then has been on the theory of *normal* brain function. You may know some of my work published in journal articles, but the more substantial parts are in monograph form, which you probably haven't read: In 1981 "Meaning and purpose in the intact brain" (part philosophy, part brain theory) in 1991 "Cortico-hippocampal interplay and the representation of contexts in the brain" (re-published on-line a few months ago); in 1996 "Axonal conduction time and human cerebral laterality"; in August this year "A theory of the basal ganglia and their disorders". Apart from the theoretical reasoning in these books, they all contain predictions, which, by now have sometimes been put to the test by others, and often, gratifyingly, have, on occasion, been found to be correct. My largest work, now on the theory of schizophrenia" is about to be made public "A neurodynamic theory of schizophrenia and related disorders", from the on-line publisher "Lulu". Perhaps after all that work on the normal brain, I may just be in a position to make cross-level reasoning also work, when applied to the abnormal situation.



Now that book on cerebral laterality from 1996 is closely related to the work on schizophrenia, because both are centred around what I call their "central hypotheses". These are fundamental statements about conduction time in populations of cortico-cortical axons. The typical response I receive when I mention these hypotheses is "This is wild speculation". End of conversation. I have had many similar smart one-line put-downs, usually from medical people, and always uttered before the speaker has grasped even the beginnings of what I'm trying to say. Occasionally, usually from science-trained researchers, I might get the query "How did you get to that conclusion?" and that opens the way to a fruitful discussion.

The third point in this section - now getting very political - is about the research environment in which many of us now have to work, which mitigates strongly against the sort of in-depth scholarship and theory construction that I advocate. Unfolding over the last twenty years, in New Zealand, Britain, and no doubt elsewhere, is a research environment where:-

*Obtaining money rather than achieving understanding of difficult and important problems becomes the primary objective. In New Zealand, all too often, research grant applications have to spell out the contributions the research would make to the country's GDP.

*Articles in high-impact factor journals, with peer review - *anonymous* of course - takes precedence over much longer scientific arguments presented in monograph form. Of course, the empirical literature on schizophrenia is so vast and so complex that any attempt to create an overall theory has zero change of being published in even the longest journal article. But monographs are now completely neglected as a form of scientific communication.

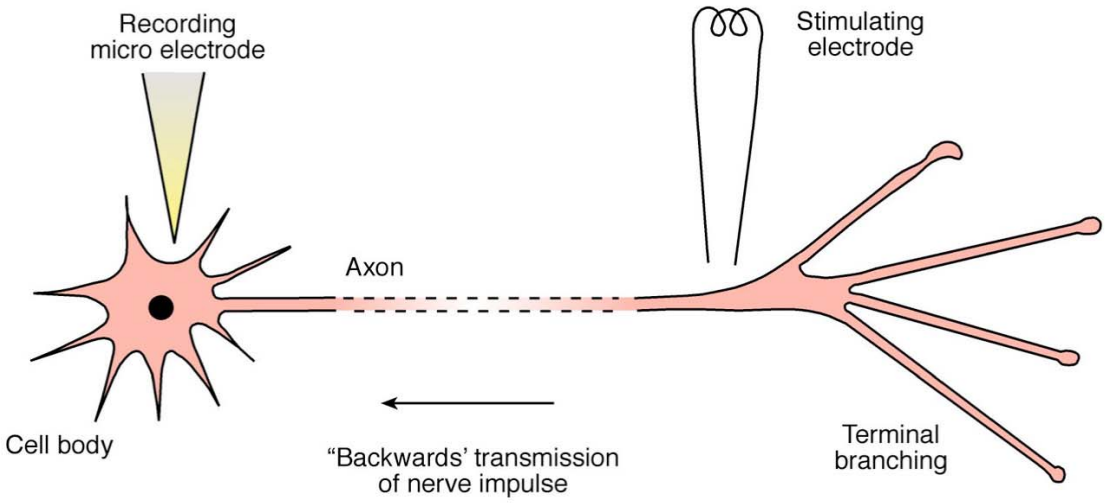
*Researchers are set up in competition with each other, to the great detriment of effective communication. But real progress in science is so difficult that we don't stand a chance unless we can collaborate and communicate freely; and the most important communication should be between dedicated theoreticians and dedicated experimentalist. Many times in recent years I have tried to engage prestigious researchers in discussion about scientific topics, to be rebuffed because they are in the middle of a grants crisis. They are always in the middle of a grants crisis. That might be taken as an indication of the excessively competitive aspects of the sociology of contemporary science. However, there is another interpretation. When rewards and punishments in any system - and it does not matter whether its crack cocaine, or gambling or the research environment - the result is behaviour which we should call "addictive". Getting those rewards dominates the whole personality, to the exclusion of everything else, so that the original object of the exercise is totally forgotten. This is also, in my view, the biggest factor driving scientific fraud.

All these are severe threats to academic freedom. At Colorado Springs last year, I had a conversation with one of the leading schizophrenia researchers from UK (I won't name him); and he said that it wasn't worth writing books "because there is no money in it", and his Dean actively discouraged researchers from writing book. Well, some of us are made of sterner stuff, and do not bend so easily to the will of university administrators, and the government ministers, whose policy they implement. As for myself, to escape all these pressures and to reclaim true academic

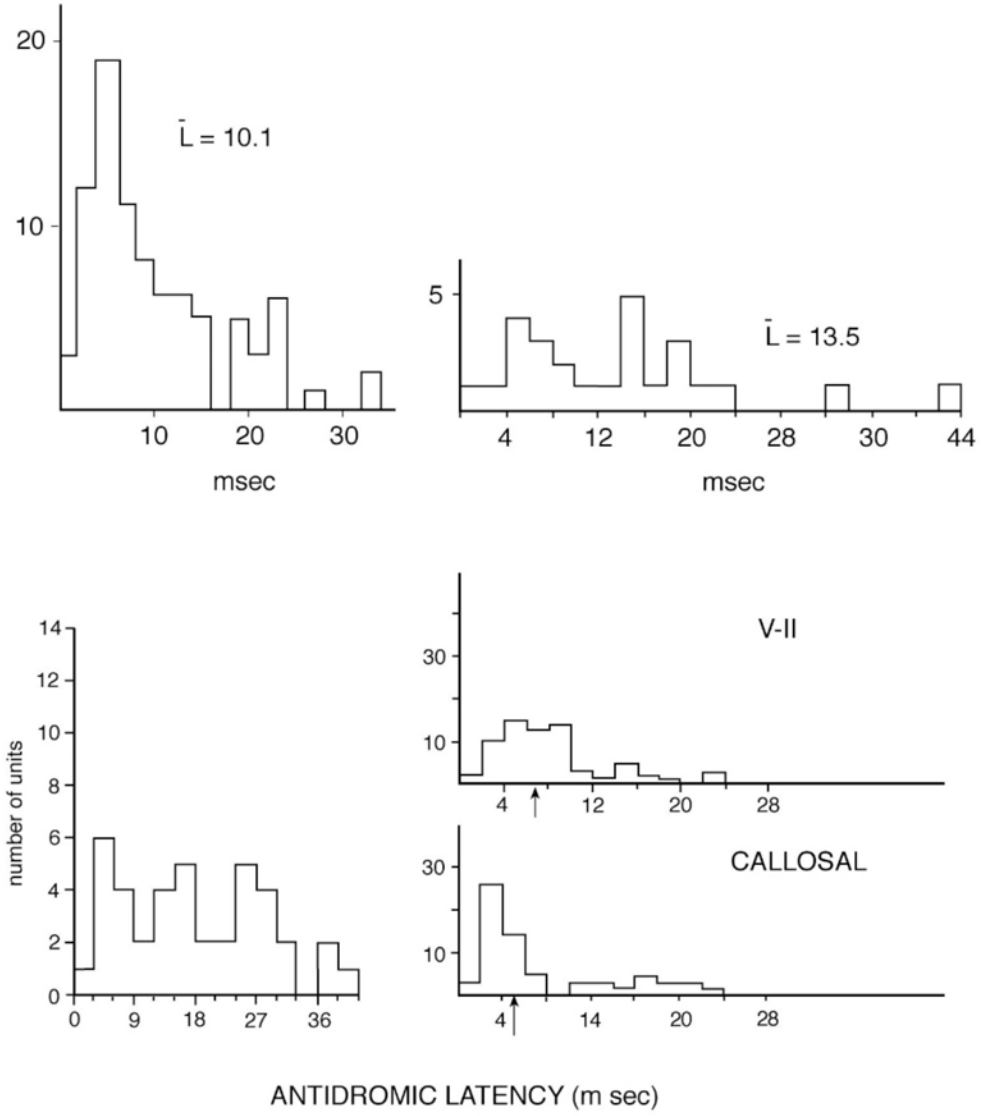
freedom, I resigned a secure university job mid-way through 1999, and have continued since then in a free-lance capacity. I am now not as wealthy as I might have been, but I'm a completely free agent, and can say what I really think in this forum with no fear of reprisal. Overall it is my view that science, in the areas I know, is now way off course, the primary motivations being personal ambition, institutional prestige, and, in the end national prestige. A large part of the industry of schizophrenia research is pursued to provide jobs for the boys, rather than fundamental understanding, and least of all, alleviation of the disablement and suffering of those with the disorder. Now, let's pause for a few moments, take our breath, and then we'll get on to the real science.

One of the ideas on schizophrenia has been that it is something to do with cerebral asymmetry - the normal differences in function between left and right hemispheres of the brain. Perhaps schizophrenia is an *abnormal variant of the normal functional asymmetry*. However, there was no real theory which explained normal left/right differences in terms of underlying neuronal processes; so it was not possible to define any abnormal variant, as a basis for the underlying the constitution from which schizophrenia arises. So, between 1990 and 1995 I worked on the theory of normal cerebral asymmetry; and, in 1996 I published the book I've referred to already ("Axonal conduction time, and human cerebral laterality"). Here, I was able to draw on the research I had done as a post-doctoral student in Oxford.

Let me say a bit about those experiments. I was recording electrical impulses from single brain cells in the cerebral cortex of anaesthetised cats.



Normally, as you will know, an impulse is generated in the cell body of a neurone, and is transmitted along the axon to the synaptic terminals. In the artificial circumstances of my experiments, I stimulated the cortical tissue some distance from the recording site, and this led to impulses being initiated in the axon, which travelled backwards to the cell body, where they were recorded - so-called "*antidromic conduction*". In this circumstance, it is possible to measure very exactly the conduction time in the relevant length of axon. Even now, more than 30 years later, not many people have made such measurements for long cortico-cortical axons. The actual results, for different populations of axons connecting together the different parts of the cerebral cortex are shown in the next figure, histograms of axonal conduction time for various axon populations, with time, in milliseconds along the horizontal axis.



The upper two diagrams are from my own experiments, for conduction distances of about 1 cm. The lower ones are from the work of Harvey Swadlow, of the University of Connecticut, who has published many papers on this subject, with basically the same design, but in rabbits, and with somewhat shorter conduction distances. The key point is that, while many axons have conduction times of only a few milliseconds, others have conduction times of several tens of milliseconds. There are many sampling biases in these experiments, all of which favour recording responses from neurones with rapidly-conducting axons. If you try to compensate for these biases, and scale thing up from animals with small brains to those with larger brains, both I and Harvey Swadlow reach similar conclusions, that, *in the human cerebrum, conduction times from cell body to synaptic terminal for long cortico-cortical axons are likely to range from ~10 msec up to 100 msec, 200 msec, or even longer*.

I emphasise the *diversity* of conduction times in any population. - and the phrase I use to capture this is *"a repertoire of delay lines"*, connecting together the different parts of the cerebral cortex. The wide diversity of conduction times is bound to have major implications for the computations done by cortical tissue, and therefore also for psychological functions. Indeed, I spoke earlier about the need for "cross-level explanations", of findings at the psychological level in terms on neuronal dynamics. For that purpose, we have a great deal of information about neuronal biophysics; but in my view, those cross-level explanation will not work unless we also include data on axonal conduction times, but if we do, they often will.

With regard to cerebral asymmetry my book in 1996 was based on what I called its "central hypothesis", that is, that, "*in the normal right hemisphere, conduction time in its nerve fibres is shorter on average than in those of the left hemisphere*. On that basis, I could explain a wide range of psychological differences between the hemispheres.

The two key observations at the psychological level which led me to that hypothesis were in the perceptual domain, that perception of consonant speech sounds gives a strong left hemisphere advantage, while perception of visuo-spatial patterns - Gestalts -gives a right hemisphere advantage. Now a consonant speech sound can be analysed as a brief sequence of acoustic events distributed over about 100 msec; so, assuming plausible values for axonal conduction times in the slower part of the range of conducting velocities for cortico-cortical axons, it could easily be imagined that a single neurone in the auditory association cortex could receive signals starting off separated in time by up to 100 msec, but arriving at the destination in the same instant of time, and so such a neurone could specifically represent the

speech sound. In contrast, for a visuo-spatial Gestalt, all the information is available in the same instant of time, and this would be represented better by neurones in a network with generally more rapidly-conducting axons.

Since 1996 I have been applying similar reasoning to try to understand the enduring non-psychotic traits which form the underlying constitution from which schizophrenia develops. As a result, I have formulated another "central hypothesis", that, "*in schizophrenia, there is a relative lack of rapidly-conducting cortico-cortical nerve fibres - those which, hypothetically give the right hemisphere its special abilities - these being replaced by more slowly-conducting ones.*"

How did I get to *that* hypothesis? It started from studying the abnormal non-psychotic traits of schizophrenia. Let me list them:

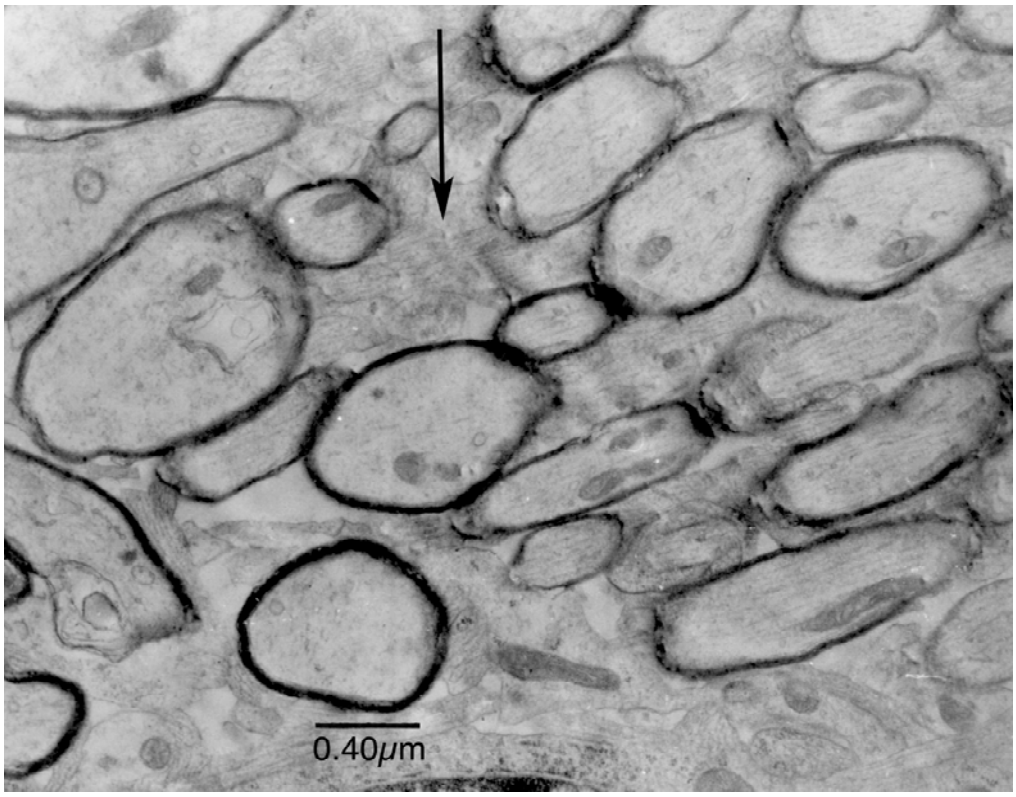
List of Schizophrenia Traits

*Impairment in perception of Gestalts (in visual, auditory and somesthetic modalities)
*Impairment in motor control by sensory guidance
Impairment in simultaneous motor coordination of many effectors
Impairment in rapid coordination between the two hemispheres
*Impairment in sustained attention/vigilance
*Impairment in semantic decoding of incoming language (sentences and longer)
Impairment in planning of semantically-coherent outgoing discourse (part of "thought disorder")
Super-normal awareness of semantic and other associations
Excessive vulnerability to distractions in various sensory modalities, and to "sensory overload"
Impairment in tasks where multiple sources of information have to be dealt with
Impairment in tasks involving shift of attentional focus
Impairment in acquisition of information from lists, etc ("rote learning")
Vulnerability to psychotic breakdowns

Most of these are impairments, but some, for instance the excessive awareness of mental associations are, in some circumstances, advantages over normal. None of them allows sharp categorical separation between schizophrenia and normal. It is also not clear to me just how disabling they can be on their own, since we seldom see them separate from psychosis, or the long-term disablement resulting from past episodes of psychosis. That is a question for the future. As I've already said, I believe we need two almost completely separate bodies of theory - one for the episodes of psychosis, based on overactivity of the messenger substance dopamine - and the other for the enduring non-psychotic traits - based, I suggest, on loss of rapidly-conducting axons. The two theories *do* overlap somewhat (see my cover illustration), and one of the most difficult questions is *"Why do episodes of*

psychosis occur in people who have all those abnormal traits?" I'll try to answer that question in a moment.

But, as regards the origin of that second "central hypothesis", in about 1997, I was struck by the fact that several of that list of traits - those marked by an asterisk - were impairments in functions normally preferred by the right hemisphere. To these can be added the classic symptom of "flattened affect". If we dissect that into its component parts, we have reduced facial expressiveness, reduced manual gesturing, reduced vocal prosody - all functions giving a normal right hemisphere advantage. So that's where that central hypothesis originated. Since then I have been surveying a great deal of other literature, psychology, psychophysiology electrophysiology, morphology, cytology - and that is all assembled in my big book.



These two "central hypotheses" started from electrophysiological studies, conducted in animals; but they also clearly have morphological counterparts, since rapidly-conducting axons have larger calibres, and are more likely to have myelin sheaths than slowly-conducting ones. This has implications for both microscopic and large scale anatomy of brain tissue. The idea of a wide diversity of cortico-cortical axons is captured in this electron-micrograph, from white matter under the cerebral cortex in the rat - the work of an Indonesian student of mine a few years ago, named Ginus Partadiredja. You

can see the wide range of axon calibres, and how some axons are myelinated, others unmyelinated. (I apologise for the low contrast, which makes the unmyelinated axons rather difficult to see.)

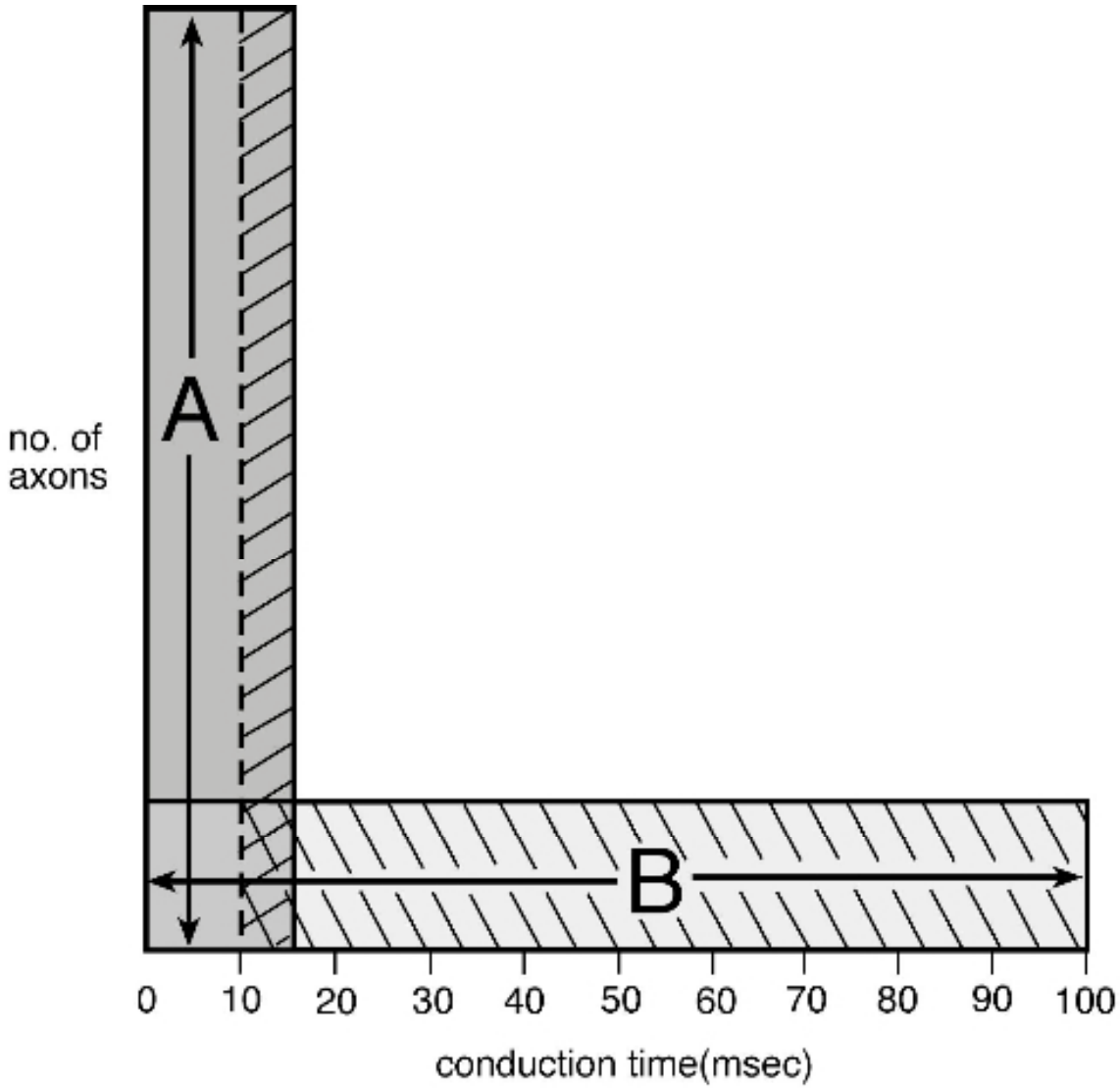
I should also emphasise that, for both these central hypotheses, one cannot establish their truth by very direct observations, because over-riding ethical constraints prevent one from doing the sort of experiments in humans - electron microscopy, or single cell electrophysiology - that can be done in experimental animals. Instead, these hypotheses have to be supported by indirect arguments, as many as possible, and particularly the psychological findings which can be explained by these hypotheses. Now I can't go into all the theory here; but I want to illustrate the way the reasoning goes with a few of the most important examples.

Some people with schizophrenia - even when well-stabilized - are impaired in recognizing visual spatial patterns. This is documented mainly in the psychology laboratory, for instance in tests of face recognition. Whether it can be documented by the sort of question a doctor might ask in a clinical interview is an important question, which I'd be happy to discuss. Now, to recognize a face, one needs to put together in one's mind all the component parts of the face, within the same instant of time. In terms of nerve cells, signals in various axons, corresponding to each bit of the face need to converge upon other nerve cells, and the messages they convey need to arrive within a very short time interval, otherwise they cannot combine their signals to produce impulses in the receiving neurons. This is possible if all the relays are along rapidly-conducting axons. But if we lose the rapidly conducting ones, to be replaced by a variety of slowly conducting ones, the convergence will not be so close together in time, and so perception will be impaired.

I use similar reasoning to account for one of the classic negative symptoms - attentional impairment, that is, poor performance in tests of vigilance. If rapidly-conducting axons are replaced by a diversity of more slowly-conducting ones, it is likely that convergence at a critical population of neurones within an instant of time will be insufficient for reliable detection of test stimuli; and as levels of alertness fluctuate, many of these stimuli may be missed, for instance in the Continuous Performance Test.

Let me now come to three related traits associated with schizophrenia - which include the *excessive ease of association, the problems with disregarding signals which are irrelevant to the task in hand, and the limitations on "processing resources" in schizophrenia*. I believe that all these can be explained in terms of my basic premise, a general loss of rapidly-conducting cortico-cortical axons, and their replacement by slowly-

conducting ones - so that conduction delays are generally prolonged, and signals more dispersed in time. The arguments are not complicated, and rest on principles from neurophysiology which go back to Sherrington in the 1920s. However, the use of these principles in the context of mental illness will be unfamiliar.



The argument goes as follows: Let’s start with those histograms, showing the distribution of conduction times in axon populations connecting together parts of the cerebral cortex, in cats, for conduction distances of about 1 cm. Now, scale this up to a brain the size of the human brain, and schematise it, and take cerebral asymmetry into account - and you get the following two histograms.

One rectangle shows a flat distribution of conduction times between 0 and 100 msec, the other a flat distribution between 0 and 15 msec. One could then consider the vertical rectangle as the distribution of conduction times in the normal right hemisphere, the horizontal one as that for the normal left hemisphere, or for either hemisphere in schizophrenia, according to my central hypothesis. Of course, I may be exaggerating the differences - but it serves to make my arguments clear. The critical aspect of the diagram is the vertical dashed line - drawn at 10 msec. I am assuming that the integration time of single pyramidal cells in the cortex is about 10 msec. Thus, afferent impulses in a population of axons reaching a cortical cell can summate to produce post-synaptic action potentials if they coincide to within 10 msec of each other. Those more dispersed in time than this will not, and will remain as subthreshold impulses confined to the presynaptic axons. In the words of C.S.Sherrington, they would be called the "*subliminal fringe*".

Envisage a brief stimulus, leading to a signal transmitted between two cortical loci. If it uses the repertoire of connections thought to be found in the right hemisphere, impulses in the majority of connections have the possibility of summating with each other to produce supra-threshold activation. If the signal uses connections thought to be characteristic of the left hemisphere, or perhaps both hemispheres in schizophrenia, a much smaller fraction of axons will convey impulses which can summate, but there will be a much large subliminal fringe.

The next step of the argument is about inhibition. Cortical inhibitory neurones receive most of their excitatory input from neighbouring cortical cells. Therefore, generally, most of the inhibition generated in the cortex depends on prior activation of local excitatory cells. So, for right hemisphere-type networks, since there is a large suprathreshold component to any signal, there will be a correspondingly large inhibitory effect following it, and so the small subliminal component is likely to have a negligible ability to combine with any other activity in the cortex, to reach threshold.

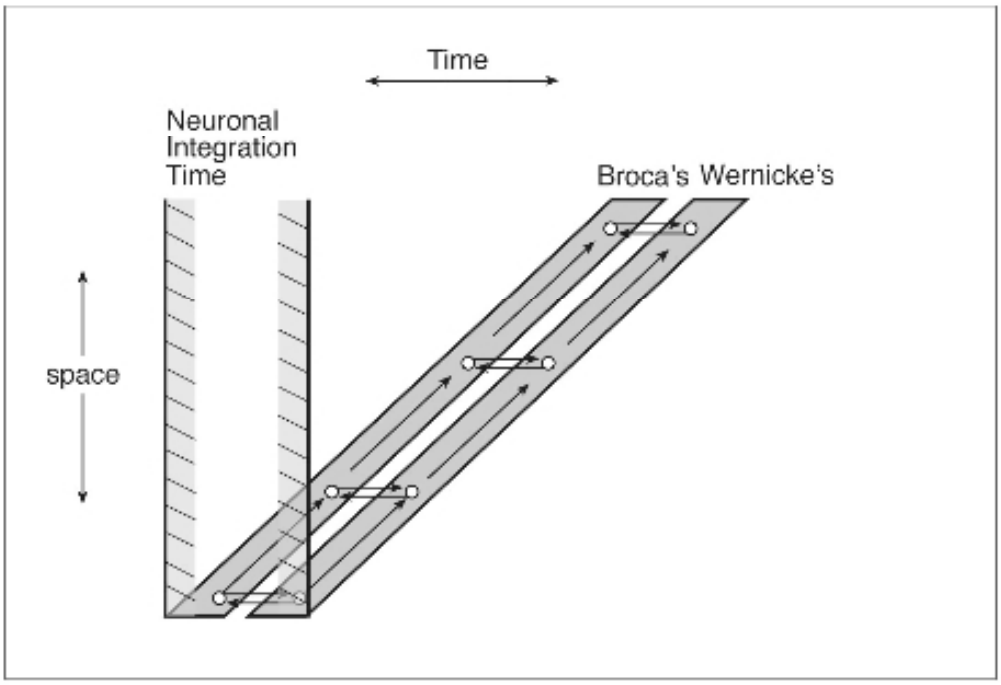
Contrast this with the dynamics of a left-hemisphere, or schizophrenia-type network. Since there is only a small suprathreshold activation, there will be little subsequent inhibition. The large subliminal fringe will not be much inhibited, and will therefore be available for summation with any other concurrent activity circulating round the cortex. In this situation, where there is a large subliminal fringe, and small supratheshold activation, the size of the subliminal fringe represents the potential for association with any other stimulus activated at the same time. *This*, I believe, is the explanation in

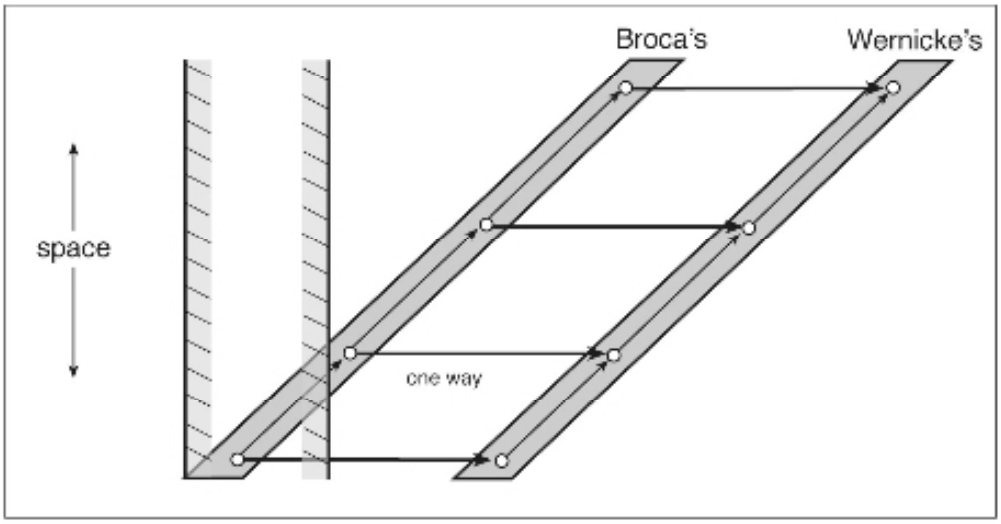
biological terms of the psychologist's finding that there is excessive ability to form mental association in schizophrenia.

There are corollaries of this argument. In circumstances where a person has to respond *separately* to one or another stimulus, rather than to form an association between them, we should find an *impairment*, rather than an advantage in schizophrenia, because foci of activation tend to interact to more than normal extent; and since mental representations held in the cortex interact to more-than-normal extent, people with schizophrenia should be especially impaired in tasks where there are many stimuli to be considered; in other words, their overall "processing resources" for cognitive operations will be reduced.

Another abnormality I wanted to discuss is the symptom of verbal auditory hallucinatons - "hearing voices". This is the most common type of hallucination in schizophrenia. It is, to be fair, partly a psychotic symptom, in that it is often alleviated by antipsychotic medications. But in many patients, the symptom persists, as an enduring trait, when, in other respects, that patient is well-stabilized - and so I ought to be able to account for it in terms of my assumption about axons. Let's think of it in neurological terms.

We generally think of Wernicke's area, in the superior temporal gyrus on the left side, as storing the acoustic representations of the speech we hear; and we think of Broca's area, in the inferior frontal region on the left side, as storing the programs for articulating the speech we utter. But sometimes, according to one body of ideas, these two sorts of representation can become intimately joined together. So, when we are having inner "verbal thoughts" - a quite normal occurrence - we use a more abstract representation: *the acoustic representation of words is intimately fused with with the program used for articulating the same words.* That means bringing neural activity in Broca's and Wernicke's areas into precisely-timed coordination. Now those two areas are some distance apart in the brain, so one can get that precise coordination only if there are nerve fibres connecting the two areas, which conduct signals quite rapidly. This is shown in the upper of these two "space-time diagrams". If these are replaced by more slowly-conducting axons (the lower diagram), the *exact coordination between the two areas will be lost*, and, subjectively, I suggest, the person will experience the "motor image" and the "acoustic image" *slightly "out of synch"*. Under these circumstances, I suggest, the inner verbal thought may sometimes seem more like a voice of external origin - the essence of an auditory verbal hallucination.

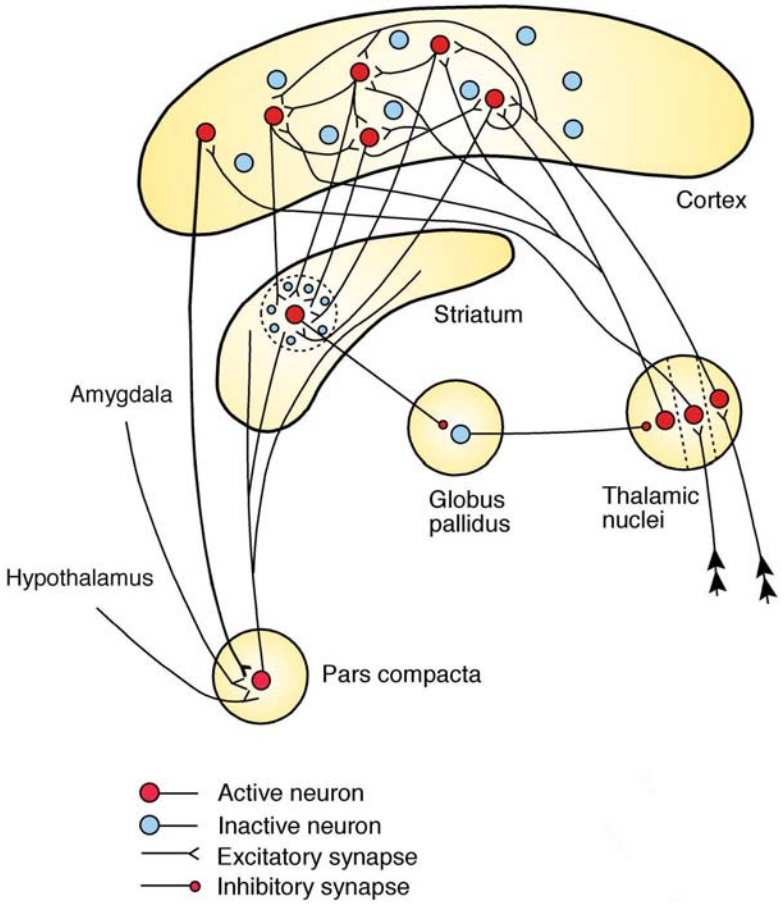




Now we come to what I have already identified as one of the hardest questions for a theory of schizophrenia. "*Why do episodes of psychosis occur in people who have some (or all) of the abnormal non-psychotic traits??*" I want to try to answer this question on the basis of my central hypothesis about axonal conduction time. This is really based on arguments already presented, but extended so that it refers to the whole of both hemispheres, rather than to individual pathways.

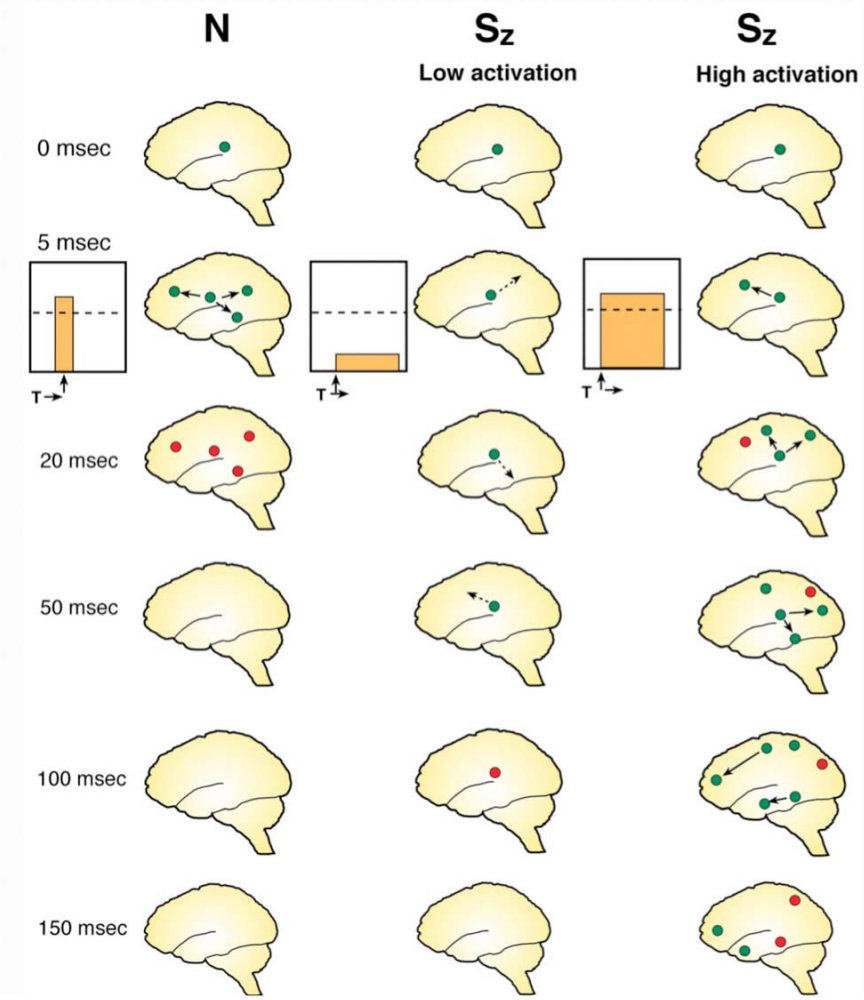
I have already suggested that the immediate cause of psychosis is an excess of neural activity in the midbrain dopamine neurons. What is driving that excess?

The firing of midbrain dopamine neurones appears to be controlled by several sets of input pathways. *First*, there are inputs from motivational centres such as the hypothalamus and amygdala, which presumably relay signals related to external events of motivational significance. However, *in addition*, there is a variety of inputs to the dopamine cells, via various routes, ultimately controlled by widespread areas of the cerebral cortex.



These pathways are probably concerned with internal or “cognitive” configurations of information, which are motivationally significant - rewarding or punishing “thoughts” if you like. It is likely that psychotic destabilization arises because of an excess of signals in these controlling pathways. So, we should try to envisage how hemispheres in which the intercommunication is generally by rather slowly-conducting axonal links - a

stable structural feature, my central hypothesis - could give rise to this sort of dyscontrol of the midbrain dopamine neurones.



Envisage a focus of excitation at a single point in the cortex, at a single point in time. Then, there are three scenarios to consider. In the case of the normal right hemisphere, depicted by the sequence of brains in the left-hand column, this focus may give rise to several secondary foci of activity, and this will occur with only short delays after the excitation of the primary focus. Any active focus will be followed quickly by a local phase of inhibition, due to relay to neighbouring inhibitory cells, so the activation of the hemispheres as a whole will quickly be subject to relatively synchronous inhibition, after which the hemispheres return to the resting state.

In schizophrenia, there are two scenarios to consider. First, in the middle column, I depict a relatively stable state, with psychosis well controlled, and only a mild level of external stimulation. Whereas in the normal brain, the

primary focus can lead to excitation of secondary foci above threshold, in schizophrenia, signals in the relays to secondary sites will undergo temporal dispersion - so the signals will not reach their destination so close together in time. Activation of the secondary foci will then often not be sufficient to exceed threshold, and there will be no persisting cerebral activity. This, I suggest, is the situation in which negative symptoms, including impaired attention, arise.

In the third scenario, shown in the right-hand column, we have schizophrenia again, but the level of external activation is much greater. Perhaps this corresponds to a recent traumatic life event. Overall activation of the hemispheres is higher than in the second scenario. When impulses are transmitted from the primary focus, they are more likely to lead to activation of secondary foci. The signals leading to this will however still be dispersed in time, and excitation will not be synchronized between different secondary foci, so rebound inhibition will be weaker, and not synchronized over the hemispheres. So, in this circumstance, activity will pass from one site to another, as a continuing state of reverberation, and cannot easily subside in the hemispheres as a whole. In subjective terms, this might correspond to a "train of thought" which cannot easily be stopped. Correspondingly, in tests of "shift of attention", such as the Wisconsin Card Sort test, there would be impairment, due to perseveration of the prevailing focus of attention. The consequence would be that the dopamine neurones in the midbrain would receive a *persisting excess* of signals descending from the cortex, rather than the normal occasional phasic signals. This, I postulate, is the circumstance in which the stable state is upset, dopamine neurones become overactive, and psychosis starts to develop.

I like to portray these arguments using a metaphor derived from the physics of Isaac Newton. The normal right hemisphere has low "inertia": It is easily set in motion, and once in motion it has low "momentum"- easily brought back to rest again. The normal left hemisphere, or both hemispheres in schizophrenia, have high inertia - sluggish to respond - but once activated, have high momentum, with a tendency to persisting high levels of activation.

So, - that has covered some of the central parts of the theory, although there is much more in my book about psychology, electrophysiology, and morphology. You may think it is all a bit idiosyncratic, and to be honest, I don't know how much of it will stand the test of time. However, there are many testable predictions, listed in one of my appendices. I want to make two final scientific points:

First, about dopamine-mediated psychosis, and antipsychotic drugs: There is a severe paradox about the receptor type involved. The theory of

psychosis which I have been developing since 1975, and which many people now hold, is that the symptoms are an exaggeration and distortion of the reinforcement function of dopamine, especially as it applies to distinctively human cognitive material - “thoughts” if you like. Evidence from basic neuroscience is now quite clear that that reinforcement function is mediated mainly by the dopamine D1-receptor, or the cyclic AMP whose synthesis it promotes in striatal cells; yet we all focus on the D2 receptor in relation to the actions of antipsychotic drugs. There are of course clinical trials which, it is claimed, refute the idea that D1 blockers have antipsychotic potency, but I and other researchers have serious questions about the adequacy of those clinical trials. This issue has been around for fifteen years. There is a barrier to progress here, which, I suggest is political, financial or legal, rather than intellectual.

Second, the science I talked about was brain biology; but that does not mean that I discount psychosocial contributions. The best evidence on that comes from study of some immigrant groups in UK and Holland. In my reading, that evidence points to a large environmental effect, at the psychosocial level, adding to genetic or constitutional factors. How could that impact on the sort of mechanisms I’ve been proposing? My guess, and it is somewhat tentative, is that growing up in a very adverse social environment could change the basic personality dynamics, so that some people acquire a *personal style of “all out striving” to succeed*. As a result, people with this unsettling upbringing, and also with the underlying constitution are more likely actually to become psychotic, by the mechanisms I have suggested, and so get a diagnosis. Without that adverse environment, many people with the basic diathesis would have a more relaxed attitude to life, and would never become actively ill. I doubt if an adverse social environment could, by itself, produce the basic diathesis.

So that’s my talk, part personal, part political, but I hope I have also given you enough on the theory I have put together, for you to get a feel for how it works. Having comprehensively insulted most of you in one section of the talk, I’m happy to go on discussing any part of it, until I run out of steam. Thank you.

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