In Search of Memory – The Emergence of a New Science of Mind.
Eric R. Kandel

Chapter 1. Personal Memory and the Biology of Memory Storage

Kandel was born in Vienna and, age 9, was kicked out of his home by the Nazi's and everything of value stolen. His father was only released because he fought in the Austro-Hungarian army in WW1.

"I cannot help but link my later interest in mind – in how people behave, the unpredictability of motivation, and the persistence of memory – to my last year in Vienna." pg 5

Kandel developed a fascination with psycoanalysis during his last year of college in 1951-52. The structure of DNA was being elucidated in 1952. Molecular biology promised the link between evolution and psycology and memory.

The science of mind is threatening to roll back the last vestige of religious dogma – but it becomes even more wonderful for it.

Memory is the core of all this.

Chapter 2. A Childhood in Vienna.

Vienna was the most important cultural center in the German speaking world – and was nourished in good part by Jews.

Hitler expected the Austrians to oppose Germany annexing Austria but the German army was welcomed by latent antiseminism – including the press.

Erics first sexual experience was with a 25 yo housemaid (almost hired to do the job)

Hitler was Austrian and had lived in Vienna. The invasion was brutal towards Jews.

"How is one to understand the sudden, vicious brutality of so many people? How could a highly educated sociaty so quickly embrace punative policies and actions rooted in contempt for an entire people?" pg 29 "One conclusion ..... the desire to destroy people outside the group to which one belongs may be an innate response and may thus be capable of being aroused in an almost cohesive group. I doubt very much that any such quasi-genetic disposition would operate in a vacuum" pg 30 "Another reason for the dissociation of cultural and moral values was the move from a cultural to a racial form of anti-Semitism: pg 30

Chapter 3. An American Education.

Eric and his brother arrived in the USA and parents followed after a second arrest – escaped by a new visa into the USA.

School at Yeshiva of Flatbush, Erasmus High School and Harvard – European History and literature.

Psycoanalysis was fascinating.

Pavlov discovered classical conditioning – association of two stimuli.

Thorndike discovered instrumental conditioning – an animal associates a behavioural response with its consequences.

Pavlov discovered two nonassociative forms of learning: habitualisation and sensitisation where the animal learns only one feature (not an association). Habitulatisation is learning to ignore a trivial stimulus and sensitisation is learning to attend to a stimulus because it is important.

These discoveries gave rise to behaviourism which limited study to those aspects of behaviour which could be publically observed and objectively quantified. (no introspection)

Freud argued that, by limiting the study of behaviour to observable, measurable actions, behaviourists ignored the most important questions about mental process.

Kandel entered medical school dedicated to becoming a psycoanalyst. He came to wonder where Freud's ego, id and superego were logated in the nervous system.

Chapter 4. One Cell at a time.

Freuds ego is the executive agency and it has both a conscious (senses, perception, reasoning, planning, pleasure, pain) and unconscious component (concerned with psycological defences, repression, denial). The id is totally unconscious and driven by the hedonistic principle of seeking pleasure and avoiding pain. The superego is the unconscious moral agency, the embodiment of our aspirations.

Grundfest (neurophysiologist 1904-1983) influenced

Kandel to progress his investigations one cell at a time.

“The biology of nerve cells is grounded in three principles .... The neuron doctrine .. states that the nerve cell, or neuron, is the fundamental building block and elementary signalling unit of the brain. The ionic hypothesis focusses on the transmission of information within the nerve cell. It describes the mechanisims whereby individual nerve cells generate electrical signals, called action potentials, that can propogate over a considerable distance within a given nerve cell. The chemical theory of synaptic transmission focuses on the transmission of information between nerve cells.” pg 60

Cajal was a most important neuro anatomist who had an “uncanny ability to infer the properties of living nerve cells from static images of dead nerve cells. He studied the brains of newborns where the neurons are less dense and utilised a special method of silver staining (developed by Golgi) which marks only about 1% of neurons, enabling Cajal to see individual neurons. Cajal indentified the cell body, dendrites and the axon.

Cajal determined that: the neuron is the fundamental structural and functional element of the brain : that the terminals of one neuron's axon communicate with the dendrites of another neuron only at specilised sites (later called synapses) : the principle of specificity which holds that neurons do not form connections indiscriminately but along specific neural pathways : and dynamic polarisation which holds that signals in a neural circuit travel in only one direction.

Cajal showed that there are three main classes of neurons: sensory neurons, motor neurons and Interneurons.

Cajal and Golgi shared a nobel prize but disagreed starkly on Cajal's interpretation. Kandel has often seen technically strong scientists who do not have the deepest insights and even the best scientists disagreeing during the early stages of discovery. Darwin pointed out that his “love of natural science .... has been much aided by the ambition to be esteemed by my fellow scientists.”

Sherrington later names the synapse and identified that nerve action is both exitory and inhibitory. (almost all inhibitory neurons are interneurons)

“A motor neuron totals up all of the exitory and inhibitory signals .... [and iff] the sum of exitation exceeds that of inhibition by a critical minimum will the motor neuron signal the target muscle to contract”

Chapter 5. The Nerve Cell Speaks.

Thinking about the signalling function of nerve cells has progressed in four distinct phases.

1. In 1791 Galvani discovered electrical activity in animals and Helm holtz measured the speed of transmission.
2. Adrian developed methods of recording and amplifying action potentials propogated along axons of sensory neurons and established that action potentials were all or nothing and that information was encoded in the frequency of spiking.
3. Bernstein developed the membrane hypothesis and determined that 70 millivolt potential across the cell membrane maintained by presenting a barrier to all ions except potassium. Bernstein also hypothesised that an action potential would be an equivalent 70 millivolts.
4. Hodgkin and Huxley investigated the axon of the giant squid and established that the action potential moved the resting potential from -70mv to +40mv. They went on to establish that the upstroke of the action potential was achieved by an influx of Na+ ions and the downstroke by an exedus of K+ ions thru channels. The resulting imbalance is corrected by a protein that transports Na+ out and K+ back into the cell.

Chapter 6. Conversation Between Nerve Cells.

In the 1940's there were two ideas regarding transmission between neurons – electrical vs chemical.

Loewi and Dale independently established that by isolating and injecting acetylcholine between cells can have an effect in the absence of an action potential.

Synaptic potentials were discovered at the synapse and they were softer than action potentials and the amplitude varied.

“The greatest strength of the scientific method is its abilty to disprove a hypothesis” pg 96

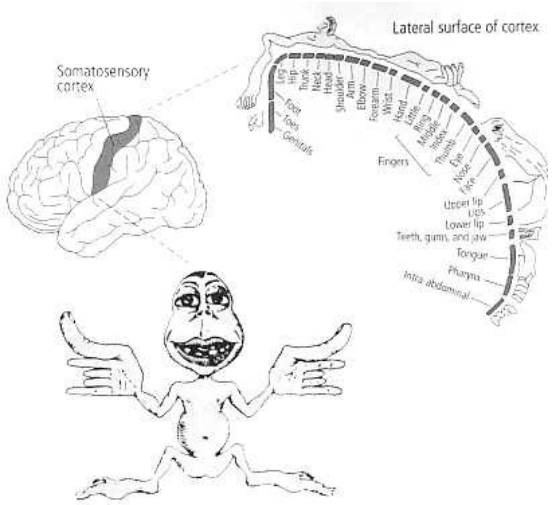
“there are two fundamentally different types of ion channels. Voltage gated channels generate action potentials that carry information within neurons, while chemical transmitter-gated channels transmit information between neurons.” pg 98

In motor neurons, the exitory neurotransmitter

released by the presynaptic neurons lower the resting membrane potential from -70mv to -55 mv while inhibitory neurotransmitter invcreases it to -75mv and in doing so adjusts the threshold for firing an action potential.
Eccles wrote “I had been encouraged by Karl Popper to make my hypothesis as precise as possible, so that it would call for experimantal attack and falsification” pg 99

Chemical synapses predominate in the brain but there are also those with electical transmission.

Katz established that the action potential leads to the opening of voltage gated calcium channels and that transmitters such as acetylcholine are released in small discrete packets (vesicles) which contain about 5000 molecules each.



Chapter 7. Simple and Complex Neuronal Systems.

“Kuffler's paper drove home the point that selecting an anatomically simple system is crutial to the success of an experiment and that invertebrate animals were a rich source of simple systems.” pg 107

Marshall was the first scientist to map the detailed sensory representation of touch and vision in the cerebral cortex.

Chapter 8. Different Memories, Different Brain Regions.

Expression of language is controlled by Bronca's area. Perception of language results from the convergence of auditory and visual information in Wernicke's area.

Penfold explored much of the cortical surface by stimulating the brains of over 1000 epileptic patients undergoing brain surgery but his results regarding memory were brought into question because the brains were abnormal and the experiences reported were indistiguishable from the hallucinations associated with epilepsy.

At the age of nine HM had an injury which resulted in increasingly dehabilitating seisures. Scoville removed the inner surface of the medial temporal lobes which cured the seisures but resulted in devastating memory loss where no new long term memories could be formed.

Milner studied HM extensively and established that “First, memory is a distinct mental function, clearly separate from other perceptual, motor, and cognitive abilities. Second, short term memory and long-term memory can be stored seperately. Loss of medial temporal lobe structures, particularly loss of the hipocampus, destroys the ability to convert new short-term memory into new long-term memory. Third, Milner showed that at least one type of memory can be traced to specific locations in the brain.” pg 129.

We now have reason to believe that long-term memory is stored in the cerebral cortex in the same area that originally processed the information.

“Milner found that in addition to conscious memory, which requires the hipocampus, there is an unconscious memory that resides outside the hipocampus and the medial temporal lobe.” pg 129
HM could learn the skill of tracing a star shape in the mirror over subsequent days though he could not remember having done the exercise on the previous day.

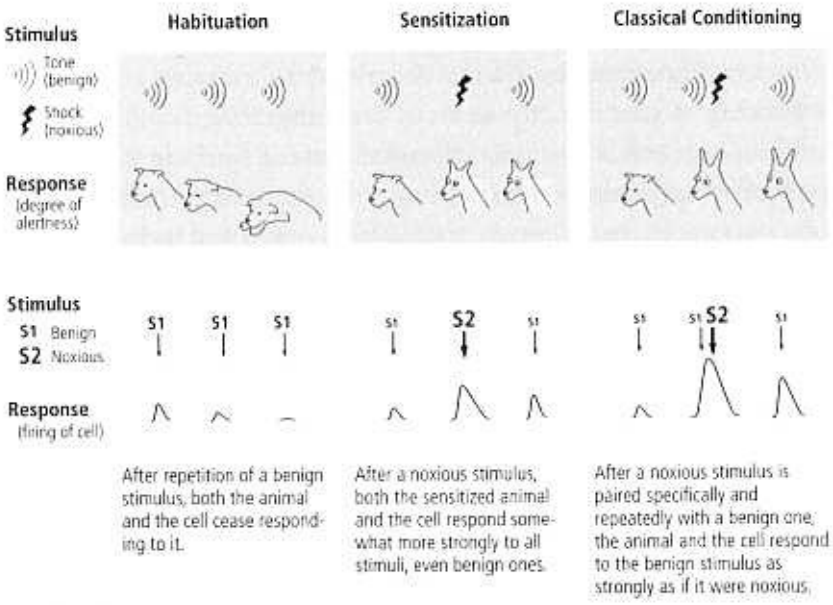
“8-6 Explicit and implicit memories are processed and stored in different regions in the brain. In the short term, explicit memory for people, objects, places, facts, and events are stored in the prefrontal cortex. These memories are converted to long term memories in the hipocampus and then stored in the parts of the cortex that correspond to the senses involved – that is, in the same areas that originally processed the information. Implicit memories of skills, habits, and conditioning are stored in the cerebellum, stratum and amygdala” pg 130

Implicit memory is the type of reflexive learning studied by behaviouralists, notably Pavlov, Thorndike and Skinner.

Chapter 9. Searching for an Ideal System to Study Memory.

Kandel, Marshall and Alden succeded in recording a neuron in a cats hipocampus. They established that a certain class of neurons in the hipocampus fire spontaneously and that action potentials in pyramidal cells in the hipocampus originate at more than one site in the cell. (probably in the dendrites) However, further experiments were attempted but difficult, time consuming and with unclear results.

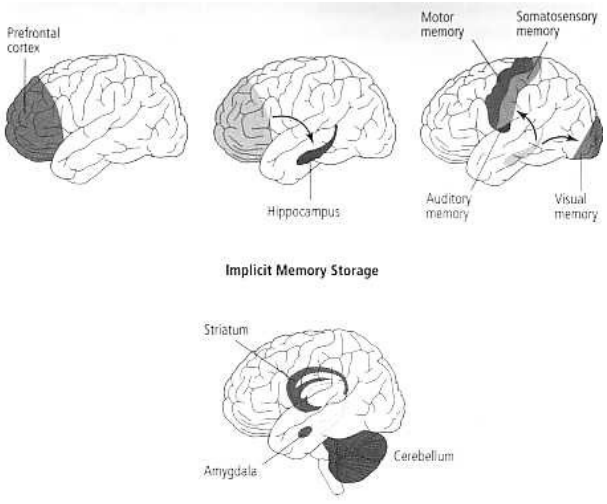
Kandel then switched to a simple system, the giant marine snail Aplysia, against the advise of his superiors.



Chapter 10. Neural Analogs of Learning.

Kandel moved to France to continue his career and experiments but was hampered by inward looking academics of the clinic where he was stationed.

Kandel also spent too much time at work!



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In 1948 Kornorski (student of Pavlov) put forward a hypothesis that the generation of one or more action potentials in a neuronal pathway in response to stimulus results in excitability (a brief rise in the threshold in the pathway – the refractory period) and that of a permanent functional transformation (plasticity).

Kandel worked with Pavlovs description of habitulisation (learn to ignore an important stimulus), sensitisation (become more sensitive due to a negative experience) and classical conditioning (associate a benign stimulus as the prediction of a negative stimulus).

Chapter 11. Strengthening Synaptic Connections.

Kandel worked with the disembodied nerve system of the Aplysia and successfully showed habitulisation, sentitisation and classicalconditioning at the cellular level.

Chapter 12. A Center for Neurobiology and Behaviour.

Mainly personal science history.

Chapter 13. Even a Simple Behaviours can be Modified by Learning.

Two aims: a detailed catalog of the behavioural repertoire of the Alysia and determine which could be modified by learning and the exploration of one of these to determine how learning occurs and how memories are stores in the neural circuitry.

Aplysia's gill-withdrawal reflex was selected – where the sensitive and vital gill is withdrawn as a response to a touch on its siphon. This simple response can be modified by habitulisation, sensitisation and classical conditioning (tail shock)

In the Aplysia, each neuron is unique and appears in the same location and Kandel was also able to map synaptic connections.

Chapter 14. Synapses Change with Experience.

How is behaviour that is controlled by a precisely wired neural circuit be changed through experience? There were at least three important existing theories. Kandel established (1970) that learning leads to a change in the strength of synaptic connections. The mapped the anatomical and functional workings of the gill withdrawal reflex, observed that habitulisation progressively reduced the amplitude of the reflex and weakened the synaptic connection between the sensory neuron and the motor neuron. And vise-vera for sensitisation.

And (1980) classical conditioning established to require the innicuous and noxious signals to arrive in precise sequence, that the sensory neurons will fire just before the noxious signals arrive, and the precisely timed firing of the sensory neuron results in a much greater strengthening of the synapse between sensory and motor neuron.

So how do genetic and developmental processes interact with experience to determine structure?

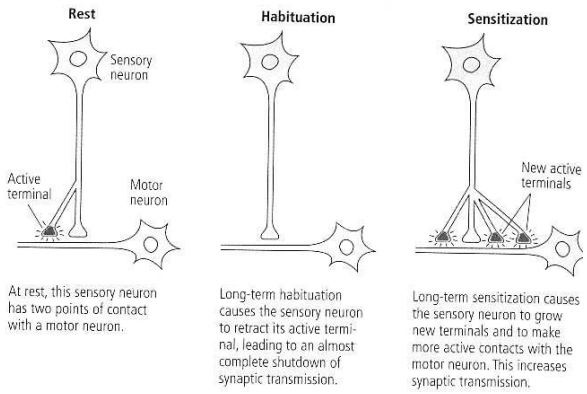
The reductionist approach allowed Kandel to establish 1.the changes in synaptic strength that underlie learning may be great enough to reconfigure a neural network 2.a set of synaptic connections between two neurons can be weakened or strengthened by learning and these changes are distributed throughout the network not at a single site and 3. in all three forms of learning, the duration of short-term memory storage depends on the length of time a synapse is weakened or strengthened. 4. the strength of a chemical synapse can be modified in two ways: Mediation (siphon sensory neurons, interneuron and motor neurons for gill-withrawal reflex) or Modulation (tail sensory neurons when acivated modulate the strength of synapses in the mediated circuit).

The dominence of chemical synapse transmission over electical may have been due to the need to evolve large and enduring changes in circuits after minimal training. (see pg 205)

Chapter 15. The Biological Basis of Individuality.

How is short-term memory transferred into long-term memory?

Eddinghaus conducted memory tests with nonsense words (RAX, PAF, WUX, CAZ etc). He found a linear relationship between the number of repetitions on the first day and the retention on the second day. Also a list of 6-7 could be learned from one presentation – longer lists required repetition. Relearning lists required less time than new lists and there was a rapid decline in retention over the first hour and a much more gradual decline over the next month.



Subsequent tests by Muller and Pilzecker along similar lines established that after learning a list, new learning presented immediately after will disrupt recall of the first but a gap of two hours between learnings will drastically reduce the disruption.

Kandel established that the same synaptic connection is involved in both short and long term learning and long-term learning involves both synaptic strength and the development of new synapses.

Merzenich established that the somatosensory cortex of monkey varies considerably with additional utilisation (training) with finger tips.

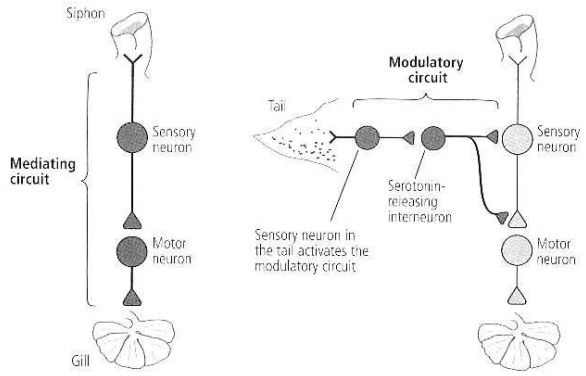
Ebert found similar results in the cortex's of violinists and cellists for the hands.

Chapter 16. Molecules and Short-Term Memory.

In Aphasia, the short-term memory change at the synapse between the sensory neuron and the motor neuron is one-sided – the sensory neuron releases more or less neurotransmitter (glutamate). The synaptic potential lasts only milliseconds but glutamate release and synaptic transmission is enhanced for minutes. The strengthening of the synaptic connection is accompanied by a very slow synaptic potential (minutes)
The shock to Aphasias tail activates a second class of neurons – these tail neurons activate a group of interneurons that act on the sensory neuron from the

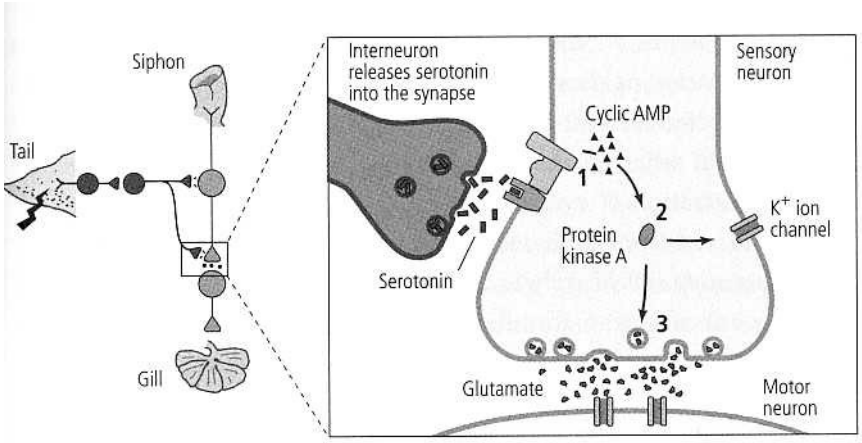
siphon. It is these interneurons that create the slow synaptic potential by releasing serotonin.

These seretonoin releasing interneurons are called modulatory interneurons in contrast to mediating circuits which produce behaviour directly.



While there are specific neural pathways, there are also specific biochemical signalling pathways.

A shock to the tail of Aphysia activates an interneuron that releases the chemical messanger seretonin into the synapse. After crossing the synaptic cleft, seretonin binds to a receptor on the sensory neuron, leading to production of cyclic AMP (1). Cyclic AMP frees the catalytic unit of protein kinase A (2). The catalytic unit of protein kinese A enhances the release of the neurotransmitter



glutamate (3).

cyclic AMP: Sutherland found that the hormone epinphrene (adrenaline) produces a brief biochemical change at the surface of fat and muscle cells and this gives rise to a more enduring change inside the cells and this is brought about by cyclic AMP. These metabotropoc receptors on the cell membrane have a section with protrudes from the outer surface which recognises intercellular siganls and a section which protrudes on the inner surface and engages an enzyme – adenylyl cyclase – which makes cyclic AMP. This acts as an amplfier via the emzyme. The chemical outside the cell is known as the first messanger and the cyclic AMP the secondary messenger.

kinese A: cycclic AMP binds to and activates an emzyme called cyclic AMP dependent protein kinase. Kinases modify proteins by adding a phosphate molecule (phosphorisation) which activates some proteins and deactivates others. Kinese is readily reversible – a biochemical switch.

The results for the Aphysia were reinforced by results from another lab working with the fruit fly (Drosophila). The cyclic AMP was originally identified in cells in the gut, kidney and liver and was now found to have a critical role in neurons of two distincly different animals. Nature simply recruited an existing efficient signallying system.

Chapter 17. Long-Term Memory

Kandel had a hunch that the synthesis of new proteins required for long-term memory formation could be tracked to changes in the genetic machinery of sensory neurons.

DNA is a dual strand of Adenine, Thymine, Guanine and Cytosine nucleotide bases. The only posssible bindings between the strands are A-T and G-C.

RNA is an intermediatory molecule with nucleotides A, G, C and Uracil. When DNA strands seperate, one strand is copied into messenger RNA which is later translated into protein.

The genetic code consists of a series of nucleotide triplets, each of which contains the instructions to form a unique amino acid. There are 4x4x4=64 possible combinations but only 20 amino acids – ie there is redundancy.

The same stretches of DNA occur in different genes and encode identical or similar regions in a variety of proteins. These recognisable regions (domains) mediate the same biological functions , regardless of the protein in which they occur.

All multicellular organisms have the emzyme that synthesises cyclic AMP, they all have kinases, ion channels etc etc

The mouse has more than 90% and the higher apes 98% of the coding sequenses of the human

genome.

Recombinant DNA involves identifying a particular gene (segment of DNA) for study, snipping it out with an emzyme, and cloning copies by inerting the gene back into the DNA from another organism such as a bacteria which divides every 20min. The final step is to decipher the protein that the gene encodes.

Chapter 18. Memory Genes.

Scheller isolated the Asphysia gene which controlles a complex behaviour of egg laying.

The Howard Hughs Medical institute was set up by Hughes and is funded by the Hughes Aircraft company which Hughes donated. Motto “People not projects”

Schacher cultured the individual sensory neurons, motor neurons and interneurons involved in the gill withdrawal reflex – with all of the precise synaptic connections intact – in tissue culture.

“Effector genes encode effector proteins such as enzymes and ion channels, which mediate specific cellular functions. Rugulatory genes encode proteins called gene regulatory proteins, which switch the effector genes on or off. ..... Regulatory proteins bind to the promotor of effector sites and thereby determine whether the effector genes are going to be switched on or off. ..... Before and effector gene can be switched on, regulatory proteins must assemble on its promotor and help to separate the two strands of DNA. One of the exposed strands is then copied into messanger RNA in a process known as transcription. Messanger RNA carries the gene's instructions for protein synthesis from the nucleus of the cell to the cytoplasm, where structures know as ribosomes translate the messanger RNA into protein. Once the gene has been expressed, the two strands of DNA zip up again, and the gene is shut off until the next time regulatory proteins initiate transcription. ..... These regulators come in two forms – repressors, genese that encode the regulatory proteins to shut gees off, and .... activators ...” pg 257

Chapter 19. A dialog between Genes and Synapses.

How is a short term memory converted to a long term memory – what are their intervening molecular steps?

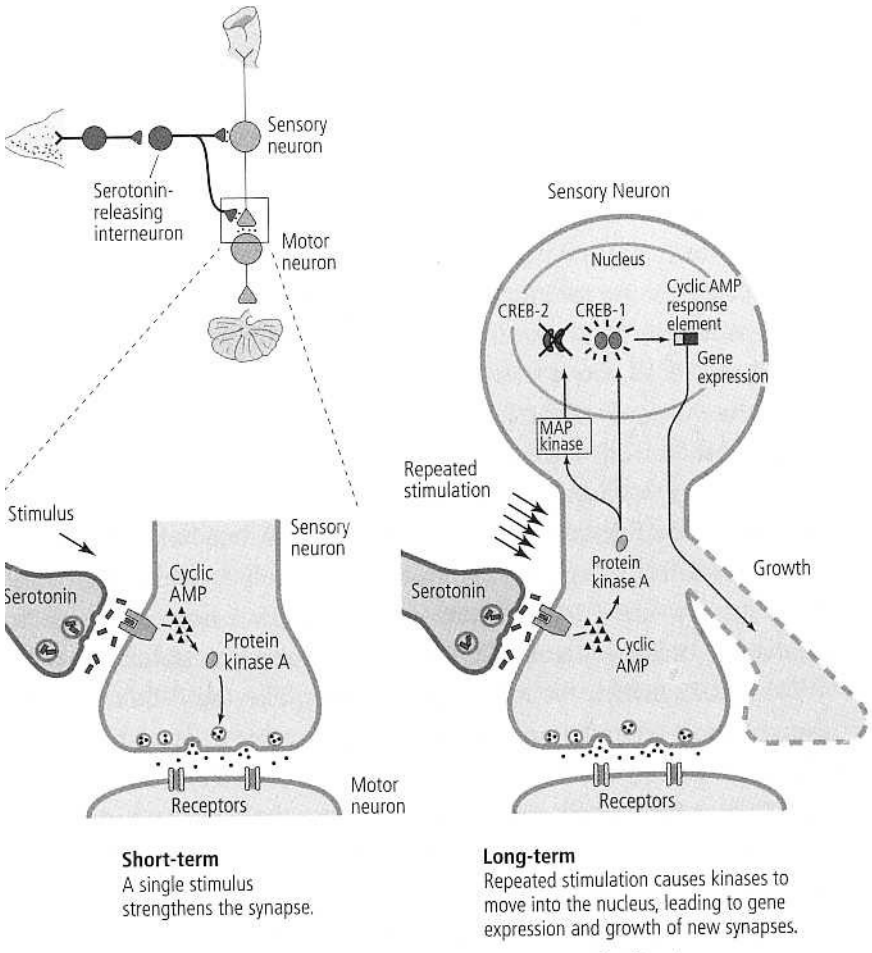
Kandel reasoned that if gene expression was required for the conversion of short-term memory at the synapse into long-term memory then the synapse stimpulated by learning somehow had to send a signal to the nucleus. Goelet and Kandel hypothesised that the protein kinase A used for short-term memory moves from the synapse to the nucleus where it somehow activates the proteins that regulate gene expression.
See 19.1

Thus, genes are not just blind instructions but respond to signals from the environment for their expression.

There are two types of CREB, one that activates gene expression, CREB-1, and one that suppresses gene expression, CREB-2.

Excitory and inhibitory signals operate at both a cellular level and a molecular level.

In time it became clear that CREB was important for



19-1 The molecular mechanisms of short- and long-term facilitation.

many forms of implicit memory in a variety of other species from Drosophila to bees to mice to people.
But, how are long-term learning and memory processes localised at specific synapses – one of 1200 synaptic terminals?

Kandel et al grew a single sensory neuron with a branched axon which formed synaptic connections with two seperate motor neurons. Using this system they established that synaptic connection can be modified independently in long-term as well as short-term memory.

There are two requirements for growth at the "marked" synapse. Activativation of protein kinase A and activation of machinery that regulates local protein synthesis (this was suprising because most protein synthesis happens in the nucleus). Proteins synthesises in the nucleus and shipped to the synapse were sufficient to initiate growth but not to sustain it.

There was a protein CPEB in the frog that performed local synthesis and a novel form of this protein was found in Aphysia. Most proteins are degraded and destroyed in a period of hours but this CPEB had Prion like qualities. Prions can fold into two functionally distinct shapes, one dominant and the other recesive. The genes which encode prions give rise to the recesive form but they can be converted to the domimant form (not easily reversed). The dominant form is self replicating – which often makes them fatal! But in a synapse this self-replication could regulate local protein synthesis to maintain newly grown synaptic terminals indefinitely.
The conversion from recessive to dominant form is controlled by seretonin.

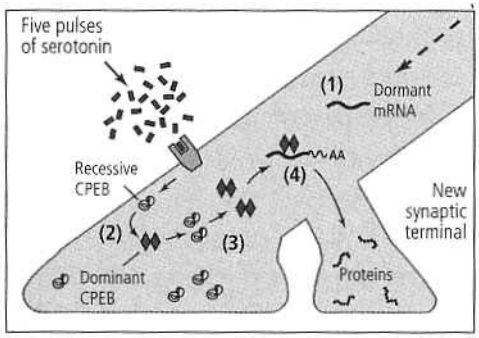
This work exposed three new principles. 1. activating long term memory involves switching on genes. 2. there is a biological constraint on what experiences get stored in memory (CREB-1 must be activated and CREB-2 deactivated). 3. The growth and maintenance of new synaptic terminals makes memory persist.

Chapter 20. A Return to Complex Memory.

"Explicit memory is far more sophistocated than the simple reflex I had studies in Aplysia. It depends on the elaborate neural circuitry of the hipocampus and the medial temporal lobe, and has more possible storage sites" pg 279

Three important breakthroughs made the next investigation possible: 1. pyramidal cells of the hypocampus play a critical role in an animals perception of its spacial environment. 2. the discovery of a synaptic strengthening mechanism in the hypocampus called long-term synaptic potentiation 3. the invention of powerful new techniques for modifying mice genetically.

O'keefe discovered that neurons in the hipocampus of a rat register information, not about a modality, but about the space surrounding the animal – "place cells".



Long-term potentiation can be intitiated by means of homosynaptic activity (in contrast to heterosynaptic mechanisms in classical conditioning – however neuronmodulators are used to switch short-term homosynaptic plasticity into long-term heterosynaptic plasticity).

Specific detail ..... the NMDA receptor functions showed that the receptor acts as a coincidence detector between presynaptic and postsynaptic events.

Chapter 21. Synapses also hold our Fondest Memories.

The method of producing long term potentiation was highly artificial and under question.. Did long-term potentiation have short and long phases like Aplysia? Use geneticly modified mice to investigate.

Until 1980 molecular genetics in mice relied on classical forward genetics - destroy one random gene in 15000, breed forwards and investigate (demanding but unbiased). Recombinant DNA techniques allowed reverse genetics - remove or introduce a specific gene and then investigate. Transgenetics involves introducing a foreign gene into a mouse egg and then bred to obtain a genetically pure strain. Another method involves "knocking out" a particular gene by inserting a segment of DNA that renders a gene dysfunctional.

Kandel blocked long-term potentiation and tested the mouses ability in well established spatial tasks.

Eg place a mouse in the center of a large white well-iluminated platform surronded by 40 holes, one of which offers escape and is marked by some symbol. The mice use three approaches in sequence, random, sequential and spacial learning. Most mice learn to use the spacial map quickly.

They found some similarities with the mechanism for implicit memory - see summary on page 292 and 293.

Chapter 22. The Brain's Picture of the External World.

Thumbnail history of cognitive psycology, behaivouralists and brain scientists into congitive neural science.

Sensory maps, in both people and monkeys, are represented in a systematic way in the cortex in proportion to the importance of the sensory peception, not the physical size.

Mountcastle, discovered that tactile sensation is made up of several distinct sub-modalities: touch includes hard pressure on the skin as well as produced by a light brush: and the neraul pathways thru the brain stem and thalamus of each are distinct. The cortex is arranged in columns and a column is dedicated to a sub-modality for each area of skin. "Mountcastle also proposed the now generally accepted idea that these columns form the basic information-processing modules of the cortex" pg 300

Retina cells do not signal absolute levels of light but rather the contrast between light and dark (small spots provide the most intense stimulus). There is a similar principal in the thalamus. However, in the cortex, most cells do not respond to small spots, but to linear contours, to elongated edges between lighter and darker edges. Each cell in the visual cortex responds to a specific orientation of such light-dark contours - and cells with similar orientation are grouped together in columns.

In addition, other aspects of visual perception are also segregated - motion, depth, form, color. An important part of the segregation occurs in the primary visual area of the cortex. This gives rise to two parallel pathways - the "what" carries information about the form of an object and the "where" information about the movement of the object in space. These pathways end in higher regions of the cortex.

Kandel discounts the existance of a cartesian theatre with a quote from Semir Zeki.

Kandel became convinced that the key to understanding the molecular mechanisms of spacial memory was understanding how space is represented in the hippocampus. London taxi drivers develop a larger hippocampus over time.

Chapter 23. Attention must be Paid.

"The brain breaks down its surroundings into many small, overlaping areas, similar to a mozaic, each represented by activity in specific cells in the hippocampus. This internal map of space develops within minutes of the rat's entrance into a new environment. ..... The general capability for forming spacial maps is built into the mind, but the particular map is not. Unlike neurons in a sensory system, place cells are not switched on by sensory stimulation. Their collective activity represents the location where the animal thinks it is." pg 309

Kandel found similar short-term and long term molecular mechanisims for spacial maps. There is a distinction between the process involved in acquiring the map and in maintaining the map in stable form for the long term.

"Despite certain similarities, the explicit memory of space in people differs from the implicit memory in profound ways. In particular, explicit memory requires selective attention for encoding and for recall." pg 311

"Attention also allows us to bind the various components of a spacial image into a unified whole." pg 312

"We found that even ambient attention is sufficient to allow a spacial map to form and become stable for a few hours, but such a map becomes unstable after three to six hours. Long-term stability correlates strongly and systematically with the degree to which an animal is required to pay specific attention to its environment." pg 312

"A modulatory pathway that has been strongly implicated in attention-related phenomena was the one mediated by dopamine. ..... The axons of the dopamine-producing neurons in the mid-brain and signals to a number of sites, including the hippocampus and the pre-frontal cortex. The pre-frontal cortex, which is recruited for voluntary action, signals back to the mid-brain, adjusting the firing of these neurons." pg 313

"In classical conditioning, for example, animals learn to associate two stimuli if, and only if, the conditioned stimulus is salient or suprising.

Involuntary attention is activated by a property of the external world. ..... Voluntary attention, on the other hand, ... , is an specific feature of explicit memory and arises from the internal need to process stimuli that are not automatically salient." pg 313

"In implicit memory storage, the attention signal is recruited involuntarily (reflexively), from the bottom up: the sensory neurons of the tail, activated by a shock, act directly on the cells that release seretonin. In spacial memory, dopamine appears to be recruited voluntarily, from the top down: the cerebral cortex activates the cells that release dopamine, and dopamine modulates activity in the hippocampus." pg 314

There are clear differences in the way men and women attend to and orientate themselves in space: women use nearby cues or landmarks while men rely more on an internalised geometric map. (the left hippocampus in men and the right paretal and prefrontal cortex in women)

Chapter 24. A little Red Pill.

A discussion of the interaction between academia and business and the rise of pharmasuitical companies importance and attraction as a career path.

"These results support the notion that the decline in hippocampus dependent learning in older animals is due, at least in part, to an age related deficit in that late phase of long term potentiation. Perhaps more important, they suggest that benign senescent forgetfullness may be reversible." pg 330

Kandels opinion "is that healthy young people are capable of studying and learning on their own and in school without the aid of chemical memory enhancers. ... Studying is without a doubt, the best cognitive enhancer for those capable of learning." pg 333

Chapter 25. Mice, Men and Mental Illness.

"By studying instinctive and learned fear in people and in experimental animals, we have gained much insight into both the behavioural and the biological mechanisms of instinctive and learned fear in people" pg 340

Kandel supports Damasio's work.

"Neural systems [inc amygdala] that store unconscious, implicit, emotionally charged memories are different from those [inc hippocampus] that generate the memory of conscious, explicit feeling states" pg 342

"One stiking feature about fear is that it can readily become associated with neural stimuli through learning. Once this happens, the neutral stimuli can be powerful triggers of long term emotional memories in people." pg 342

Chapter 26. A New Way to Treat Mental Illness.

Schizophrenia is characterised by three types of symptoms: positive (min 6 mths, delusions, hallucinations and illogical thinking), negative (chronic, social withdrawal, poverty of speech, loss of ability to feel and express emotions) and cognitive (poor attention, deficits in explicit short-term memory critical to planning). Caused by excessive dopamine transmission. All medications target the particular D2 dopamine reseptor. There is a genetic disposition for an unusually large number of D2 receptors in the stiatum and these exert their impact early in development, often prior to symptoms being apparent - and currently irreversible damage.

Depression is characterised by an unpleasant mood that is present day in and day out for a majority of the time, as well as intense mental anguish, inability to experience pleasure, and a generalised loss of interest in the world. Effective drugs act primarily on two modulatory neurotranmitters: seretonin and norepinephrine. It is not known why SSRI drugs have an immediate molecular effect but a emotional effect delayed by 3 weeks.

Chapter 27. Biology and the Renaissance of Psychoanalytic Thought.

Psycoanalitics never really managed to move from theory to an experimental emperical medical disipline. However....

Beck developed, tested and documented Cognitive Behavioural Therapy which is usually as effective as antidepressent medication in treating people with mild and moderate depression and in some studies it appeared superior in preventing relapses. It has also been extented to anxiety disorders and others. Becks found that people with depression almost invariably have unrealistically high expectations of themselves, overreact dramatically to any dissapointment, put themselves down wherever possible, and are pessimistic about their future.

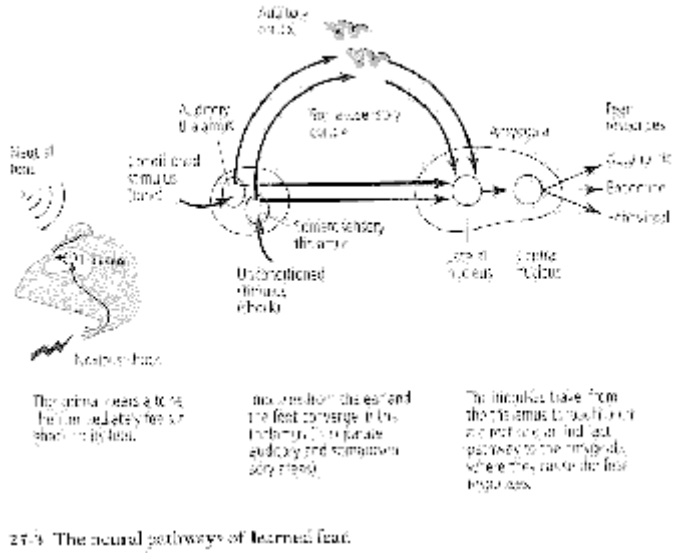
Klerman and Weissman created a second scientifically valid form of short-term therapy:

Interpersonal psycotherapy which focusses on correcting patients mistaken beliefs and on changing the nature of their communication with others.

Interpersonal Therapy seems particularly effective in situational crisis and CBT appears to be particularly effective in treating chronic disorders.

Kandel believes that a biological approach is required for psycotherapy.

Drugs alone are not effective - many patients do better with drugs and therapy and a suprising number do well with therapy alone.



27-3 The neural pathways of learned fear.

Chapter 28. Consciousness.

Consciousness is a difficult problem! Need a definition. Noted contributions by Christof Koch, Plato, Descartes, Dennett, Searle and Nagel (and others).

Searle and Nagel ascribe two characteristics to the conscious state: unity and subjectivity. Unity may not be insurmountable but subjectivity is formidable because by definition it is internal.

Crick was very interested in the claustrum as a neural correlate of consciousness. It is a thin sheet of brain tissue located below the cortex and very well connected to sensory areas, motor areas and the amygdala.

Ekman has shown that irrespective of sex or culture, conscious perceptions of seven facial expressions (happiness, fear, discust, contempt, anger, suprise and sadness) have virtually the same meaning to everyone.
These seven expressions invoke prominent activity in the amygdala (the structure that mediates fear. "What was suprising was that conscious and unconscious stimuli affected different regions of the amygdala, and they did so to differing degrees in different people, depending on their baseline anxiety. .... Unconscious perception of fearful faces activated the basolateral nucleus ..... in direct proportion to basline anxiety. ....Conscious percetion of fearful faces, in contrast, activated the dorsal region of the amygdala, which contains the central nucleus, and it did so regardless of a persons background anxiety." pg 387

"Unconsciously perceived threats disproportionately affect people with high background anxiety, wheras consciously perceived threats activate the fight-or-flight response in all volunteers." pg 387

Libets experiments regarding free will were summarised (monitoring brain potential which preceeds voluntary action)

Chapter 29. Rediscovering Vienna via Stockholm.

A summary of Kandels experience in receiving the Nobel Prize

The Austrians have never properly achnowleged their proactive role in antiseminism and the WWII holocaust and Kandel is becoming very vocal about it (about time).

Chapter 30. Learning from Memory: Prospects.

Collaboration in USA science is egalitarian and great
A career in science is not easy - people avoid risks and uncharted territory and are often slow to accept new evidence that does not conform to their views
The next steps in understanding the brain require tools to focus at the neural network level as they relate to complex cognitive functions.

Kandel has three interesting questions 1) to understand how unconscious processing of sensory information occurs and how conscious attention stabalises memory 2) the relation of unconscious to conscious mental processing in people 3) applying molecular biology to link molecular biology of mind to sociology.

Kandel benefitted considerably from his psychiatric training which he did not use directly as a foundation to his investigations.

Kandel encourages new graduates to get

involved in experimental activities rather than just persuing additional course work. It is also important to be bold and tackle difficult problems that initially appear messy and unstructured. And it is very important to define a set of problems that has a long-trajectory to avoid getting bored.