

Our final session deals with two ways in which the human mind can confront the difficulties of life: madness and wisdom.

Anxiety is crucial to our understanding. We go mad or we become wise depending on our ability to handle it. Munch's painting of *The Scream* represents the terrible feeling of anxiety – the sense of doom that comes upon us when we feel something is significantly wrong but we have no idea about what it is or how to react.

Anxiety is currently studied by psychologist and psychiatrists. However, the modern use of the term began with the Danish philosopher Søren Kierkegaard who interpreted anxiety in religious terms – as deriving from our freedom to choose when we cannot know all the consequences of our actions. These ideas persist today in existential therapy and in religious counseling. Paul Tillich defines three aspects of anxiety – not being able to live forever, not being able to understand, not being able to do the right thing.

Psychoanalysts have thought of anxiety as repressed sexual libido, pharmacologists have attributed it to an imbalance in the brain's neurotransmitters, behavioral psychologists have considered it a response to stress.

Brain and Mind: Course Outline

1. Introduction. Brain anatomy. Stroke. Neurons. Excitation. Action potentials. Synaptic transmission.. Body sensations. Braille.

2. Moving to the Music. Muscles. Stretch reflexes. Basal ganglia. Cerebellum. Parkinson's Disease. Balance. Hearing. Speech and music.

3. Sensation and Perception. Taste and smell. Hunger and satiety. Vision. Visual fields. Motion. Recognizing faces and objects. Illusions.

4. Consciousness. Sleep, meditation, coma, epilepsy. Locked-in syndrome. Attention. Consciousness. Theory of mind. Split-brain studies – interpreter.

5. Learning and Memory. Synaptic changes. Motor skills. Priming. Episodic vs semantic memory. Amnesia. Alzheimer's Disease.

6. Language and Emotion. Language. Humans vs chimps. Aphasia. Dyslexia. Basic emotions. Autonomic Nervous System. Love and Hate. Music.

7. Thought and Will. Executive functions. Psychopathy. Brain networks (attention and default). Determinism. Free will.

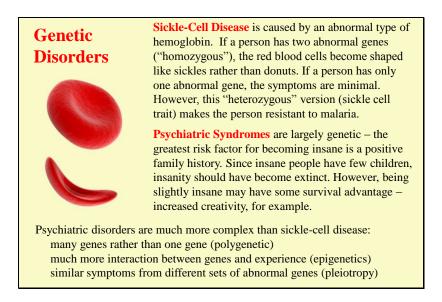
8. Madness and Wisdom. Psychiatric diagnosis. Anxiety. Schizophrenia. Depression. Addiction. Maturation of brain. Mental speed. Ageing. Wisdom.

Psychiatric Diagnosis	
The diagnosis of mental disorders usually follows the categories provided by either the DSM-5 or ICD-10.	DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS HTHE EDITION
Diagnoses are characterized by	and the second se
"reliability" – how well different assessors agree	
"validity" - how accurately the disease is identified	
Reliability is good for the main categories of mental	AMERICAN PSYCHIATRIC ASSOCIATION
illness. Since psychiatric diagnoses cannot be checked	
against any "gold-standard," there is no true validity.	The ICD-10 Classification
Some of the main categories:	of Mental and Behavioural
anxiety disorder	Disorders
schizophrenia	Clinical
bipolar disorder	and diagnostic guidelines
depression	
autism	(()
personality disorder	World Health Organization Generation

There are two systems of psychiatric diagnosis – the Diagnostic and Statistical Manual of the American Psychiatric Association and the International Statistical Classification of Diseases and Related Health Problems. Two blue books.

The main problem with diagnosing mental disorders is that we do not have any gold standard for the diagnosis. No specific finding on autopsy or biopsy, no specific blood test, no specific genetic abnormality. Nothing defines any of the mental disorders that we diagnose. Rather, the diagnosis is based on sets of symptoms.

We shall consider anxiety disorders, schizophrenia, and the affective disorders. We have already briefly mentioned autism when we discussed theory of mind (session on consciousness) and personality disorders when we considered psychopathy (last week).



Psychiatric disorders run in families – there is a large hereditary component. However, the genetic causes of mental disorders are very complex.

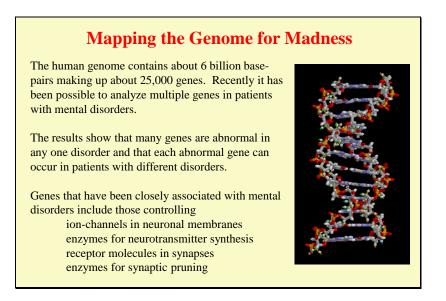
Sickle-cell disease allows us to consider the basic concepts of inherited disorders. The genetics of this disorder are simple.

1. the disease is caused by an abnormal gene that causes the blood cells to become shaped like sickles rather than donuts. This can block capillaries causing infarctions. The disease usually presents in childhood with attacks of pain.

2. during evolution the disease should have died out since people with the disease will not produce as many children as those without.

3. the disease is "recessive" – it requires two abnormal genes (one from each of the parents). If there is only one abnormal gene, the hemoglobin is a little abnormal but not enough to cause severe symptoms – the person has "sickle-cell trait"

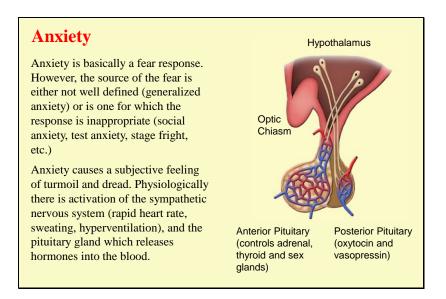
4. however, the hemoglobin in sickle cell trait makes the person resistant to malaria – the parasite cannot complete the part of its life-cycle that it spends in human red blood cells. This survival advantage ensures that the genetic abnormality persists in the population.



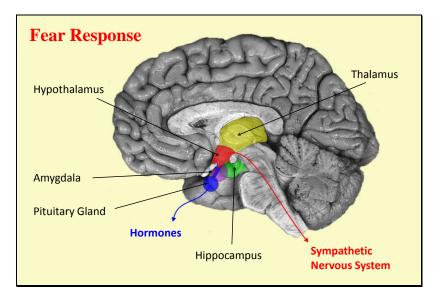
In recent years there have been many genetic studies of patients with mental disorders. However, there is no clear link between any one gene and abnormal behavior.

Psychiatrists published the first Diagnostic and Statistical Manual in 1952. At that time, chlorpromazine was first being used in psychosis and Watson and Crick were about to describe the double helix. The dream was that each precise category of mental disease would be associated with one abnormal gene controlling one neurotransmitter and that each disorder could then be cured with a drug to counteract the abnormal transmitter levels.

Mental disorders are far more complex than we dreamed.



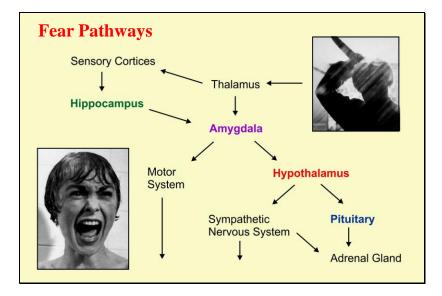
Anxiety is a fear response without a clear or appropriate source of the fear.



The fear response is important for human survival.

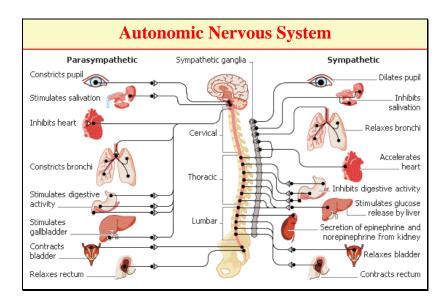
The main center the brain controlling the fear response is the hypothalamus. Its outputs go to the sympathetic nervous system and to the pituitary. Stimuli activate the fear response through the thalamus.

The hippocampus and amygdala are involved in learned fear responses, such as those involved in post-traumatic stress disorder.



This shows the pathways involved in the fear response. The photographs are from Alfred Hitchcock's *Psycho* (1960) starring Anthony Perkins and Janet Leigh.

Stimuli are processed in the thalamus. Further analysis and comparison to memory occur in the sensory cortices and hippocampus. The amygdala may be rapidly activated from the thalamus or more slowly activated from the hippocampus. The full fear response involves motor activity and changes in the internal organs mediated through the sympathetic nervous system and through hormones.



Third time for this slide – we have seen this before when we discussed our appetite for food, and when we considered emotions. The autonomic nervous system controls our internal organs. Little of their activity reaches consciousness. Our insides follow their own rules.

Emotions such as fear change these activities greatly. Our heart beats faster, our mouth goes dry and our pupils dilate when we are emotionally aroused.

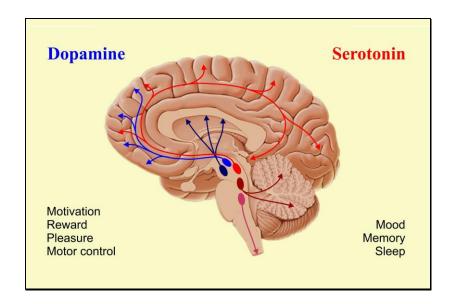


Anxiety is best treated with psychotherapy – the "talking cure" invented by Josef Breuer, Sigmund Freud and Bertha Pappenheim.

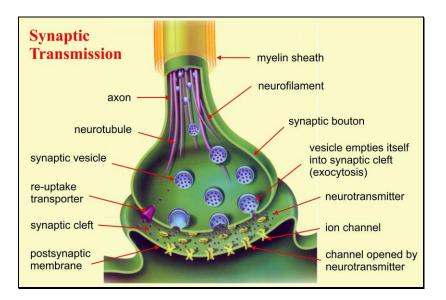
This is Freud's couch. It is in Freud's house in London, but it is very Viennese. It has witnessed many stories – Dora who lost her voice, the Wolf Man who dreamed of a tree full of wolves, and little Hans who was afraid of horses.

Psychotherapy is the treatment of choice for anxiety. Behavioral therapies involve learning new techniques to prevent or counter anxiety. One recently popular technique is mindfulness-training. Psychodynamic therapy attempts to change the personality by studying its development. Psychotherapy can also be obtained from religious counselors or friends. Talking to a compassionate objective listener is the most important part of psychotherapy.

Several drugs can be used to attenuate anxiety. Most commonly used are the selective serotonin re-uptake inhibitors like Prozac. Diazepam (Valium) can be used for acute panic attacks but there is a danger of withdrawal in the drug is used for prolonged periods. Stopping the drug can then produce the anxiety that it was used to treat. Sometimes people may use a drug such as propranolol (Inderal) to block the palpitations that occur in stressful situations like public speaking.

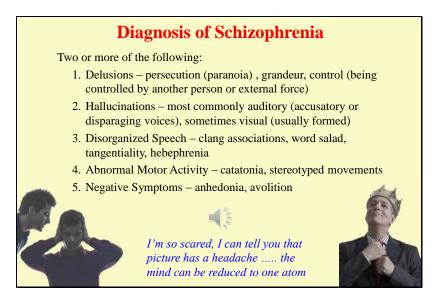


Mental disorders are often associated with changes in the brain's monoamine systems. Dopamine is involved in motivation and motor control. Serotonin participates in mood and sleep.



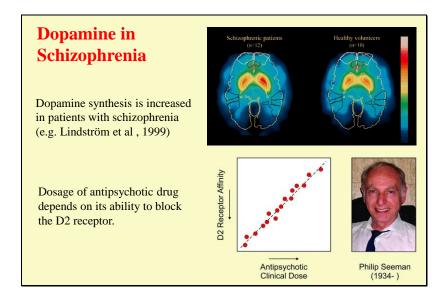
Psychopharmacology attempts to change the mind by altering the metabolism of neurotransmitters. Particularly important are the monoamines such as dopamine and serotonin. Medications can alter the actions of these transmitters in a variety of ways:

- increase exocytosis e.g. amphetamine
- block enzymes that break down the transmitter e.g. monoamine oxidase inhibitors such as Parnate
- block the carriers that take the transmitter back up into the presynaptic bouton, e.g. "tricyclics" such as imipramine, more selective drugs (selective serotonin reuptake inhibitors) such as Prozac or Zoloft



These are the main symptoms of schizophrenia. Hebephrenia is childish (actually adolescent) talk.

The recording is from a young schizophrenic patient. He demonstrates very loose associations that are sometimes almost poetic. His pseudoscientific explanation of the mind is typical of schizophrenic delusions.



Dopamine abnormalities in schizophrenia may themselves be secondary to abnormalities in other transmitter systems. For example, there might be increased activity in the brain's glutamate system. Another recent paper has implicated hyperactivity in the brain-systems that prune unused synapses. This might explain the loss of nervous tissue in schizophrenic brains and the abnormally simplified cognitive responses. Philip Seeman is a pharmacologist at the University of Toronto.



The video by a young schizophrenic recounting his first experience of hearing voices.

https://www.youtube.com/watch?v=Lw-IDTyxSrM

The audio recording gives a simulation of the auditory hallucinations that can be experienced by a schizophrenic patient. Several different voices are heard. They reflect the paranoia and the delusion of worthlessness.

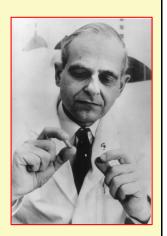
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Treatment of Schizophrenia

Most important is the use of "tranquilizer" phenothiazine drugs, which bind to the D2 receptor and reverse the effect of excess dopamine.

These were initially synthesized in the dye industry. They were found to have an antihistamine effect. Then they were used as a sedative, and finally tried in psychotic patients in the early 1950s. This totally revolutionized the treatment of schizophrenia.

In addition, the patients need extensive social support to overcome their tendency to isolation.

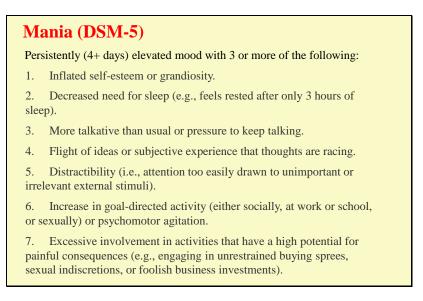


Heinz Lehmann (1911-1999)

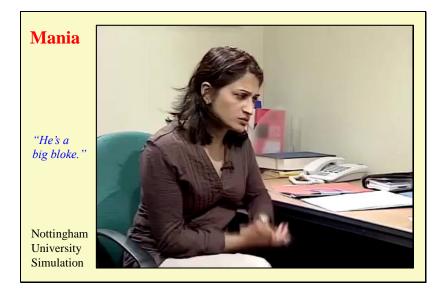
Chlorpromazine was initially used as a sedative in France. Some French psychiatrists used the drug to sedate psychotic patients and found that it decreased their madness without putting them to sleep – sedation without narcosis.

Heinz Lehmann, a psychiatrist at the Douglas Hospital in Montreal (then known as the Protestant Hospital for the Insane, was the first psychiatrist to use chlorpromazine in North America. He had fled Nazi Germany in 1937 because his father was Jewish. He came to Canada ostensibly for a skiing vacation. He became the clinical director of the Douglas Hospital in 1947.

Chlorpromazine revolutionized the treatment of psychiatric patients, who could now be discharged from hospital. The hospitals were emptied out. Unfortunately many of the patients did not continue to take their medication. So we now have many crazy people on the streets.



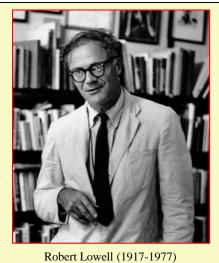
Mania is the disorder that is perhaps most typical of "madness." The patients are overtly "crazy."



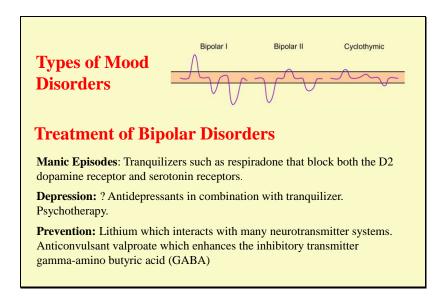
This video shows a simulated interview (University of Nottingham) between a psychiatrist and a manic patient. He is trying to convince her that he has a cure for cancer.

https://www.youtube.com/watch?v=zA-fqvC02oM

... I ran about the streets of Bloomington Indiana crying our against devils and homosexuals. I believed I could stop cars and paralyze their forces merely by standing in the middle of the highway with my arms outspread. Bloomington stood for Joyce's hero and Christian regeneration. Indiana stood for the evil, unexorcized, aboriginal Indians. I suspected I was a reincarnation of the Holy Ghost, and had become homicidally hallucinated. To have known the glory, violence and banality of such an experience is corrupting

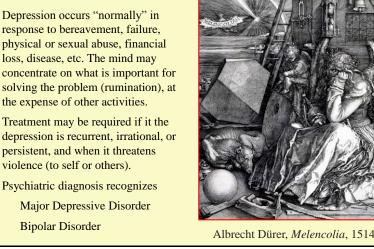


Many creative individuals have suffered from affective psychoses. Robert Lowell was one of the great American poets of the mid 20th Century. Here he describes one of his manic episodes. He has a flight of ideas – from Bloomington to Leopold Bloom in *Ulysses*, from Indiana to Indians. Though one feels glorious during the manic phase, the actions are actually quite banal. You were not the genius or hero that you thought you were.



Bipolar disorders are extremely difficult to treat. It is so easy to tip someone who is manic into severe depression, and then suicide is a very significant risk.

Depression



Mild depression may cure itself, when the mind works through the problems that it is facing.

Major Depressive Disorder (DSM-5)

Five or more of the following symptoms present for 2+ weeks:

- 1. Depressed mood most of the day.
- 2. Markedly diminished interest or pleasure in all, or almost all, activities.
- 3. Significant weight loss when not dieting or weight gain
- 4. Insomnia or hypersomnia.
- 5. Psychomotor agitation or retardation nearly every day
- 6. Fatigue or loss of energy nearly every day.
- 7. Feelings of worthlessness or excessive or inappropriate guilt.
- 8. Diminished ability to think or concentrate, or indecisiveness.
- 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

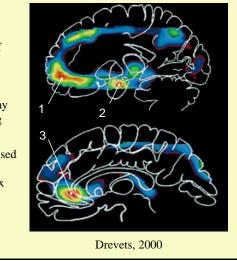
Major depression requires treatment. The psychiatrist must be very sensitive to any suggestion of suicide.

Suicide accounts for about 1% of all deaths. It is common in adolescents and young adults, where it is the second most frequent causes of death (accidental death is the first). It is also common in old age, often related to social isolation, and decreasing cognitive abilities.

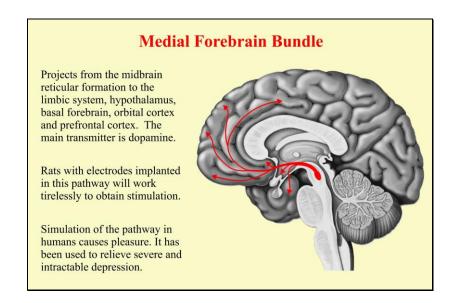
Depression

The emotional brain consists of many interacting systems. Variations in the different monoamine transmitters, their receptors and their enzymes may lead to some systems becoming inappropriately overactive.

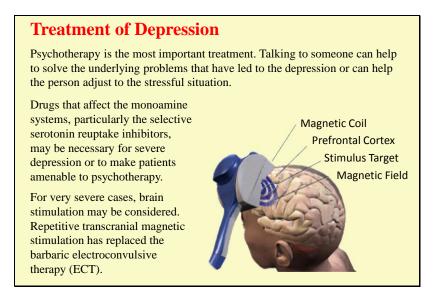
The brain of moderately depressed patients shows increased blood flow in the orbital frontal cortex (1), the amygdala (2) and the anterior cingulate gyrus (3).

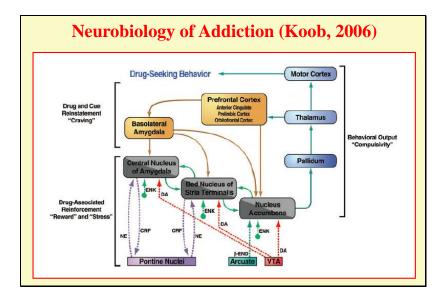


Depression involves increased activity in the orbitofrontal cortex and the amygdala and the anterior cingulate gyrus. Electrical stimulation in the orbital regions of the frontal cortex may help severe intractable depression. How this works is not known. It may interfere with obsessive rumination or it may activate the medial forebrain bundle to release monoamines.

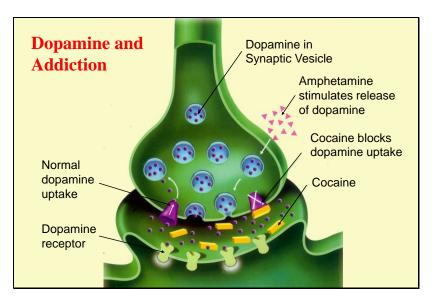


The medial forebrain bundle is a very important pathway for the emotions.





This is a complicated slide and you do not need to know all the details. It suffices to know that there are several brain systems that are involved in reward or stress – these use neurotransmitters such as dopamine (DA), norepinephrine (NE) and encephalin (ENK). Addictive drugs alter these systems giving the subject a feeling of intense pleasure – a "rush," or a sensation of "riding the tiger." The various parts of the motor learning system learn activities that bring about these feelings – compulsivity. The emotional regions of the brain learn to trigger such behavior – craving.

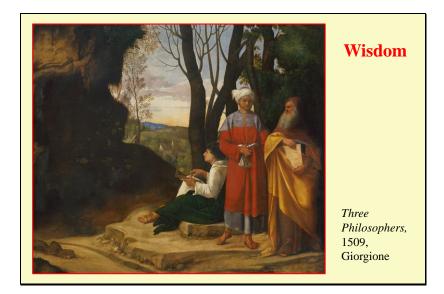


This slide shows how the addictive drugs amphetamine and cocaine work. Amphetamine triggers the release of dopamine.

Cocaine blocks the uptake of released dopamine from the synaptic cleft.

Both drugs increase and prolong the effects of dopamine at the synapse.

Dopamine is the main transmitter in the medial forebrain bundle – the pleasure pathway.



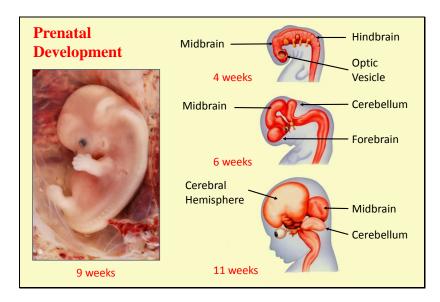
The course is winding down. Some words of wisdom before you go.

What the painting represents is not clear. Most consider it a representation of three philosophers. Perhaps an ancient Greek philosopher like Plato, an Arabian thinker like Avicenna, and a Renaissance writer like Giovanni Pico della Mirandola.

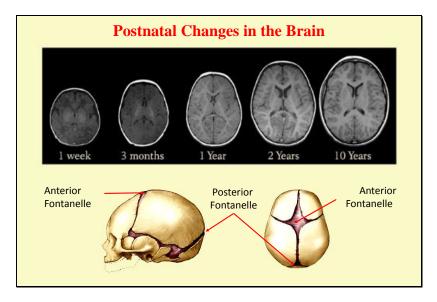
The subject of their philosophy is a dark cave. Whether this represents ignorance or mortality is unknown.

Some say that the three philosophers represent the three ages of man.

So how do we accumulate wisdom as our brains get older?

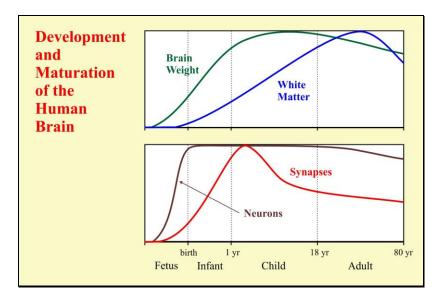


Let us begin in the womb. This shows the brain in a 9-week fetus. You can see the optic vesicle that will make the eye (dark-colored) and the otic vesicle that will make the ear (light). The brainstem is bending, the cerebellum is sprouting and the cerebrum is just beginning. The cerebral hemispheres begin to expand over the rest of the brain after 4 weeks and continue to expand until birth.



After birth the brain grows rapidly until the age of 2 years when it is about 90% adult size.

The growth is allowed by the elastic fontanelles between the skull bones. The posterior fontanelle closes by about 3 months and the anterior closes at about 18 months.



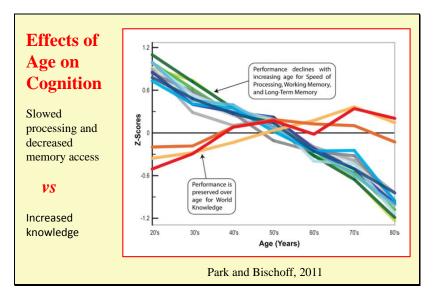
The brain keeps growing until our mid-teens and then slowly decreases in size. The time scale is not linear – I have spread out the earlier times and compressed the later.

The number of neurons (brown) does not change much after birth. A few die and are replaced. Yet basically we have the same neurons now that we were born with. They do not replicate like other cells in the body. At least that is the main rule. Recently there have been some studies showing that some neurons might replicate but these are few. Although neurons do not generally replicate, they can regenerate their processes if the cell bodies are preserved. After middle age the neurons slowly start to die off.

The number of synapses (red) increases until the age of about 3-5 years. During these early years we learn more rapidly than at any other time in our lives. We learn to walk and run, to speak and think, we start to remember. And we become aware of ourselves. After the age of 5 years the number of synapses are pruned as we learn which ones work best. Proliferation and Pruning.

Myelination of pathways, which speeds the transmission of information, continues into adulthood, with the frontal lobes being the last to myelinate fully (by about age 30).

I am afraid I cannot sugar-coat reality - nothing gets bigger, better or faster after about 60 years of age. Our only consolation is that we think that we become wiser but we are not sure how to measure wisdom.

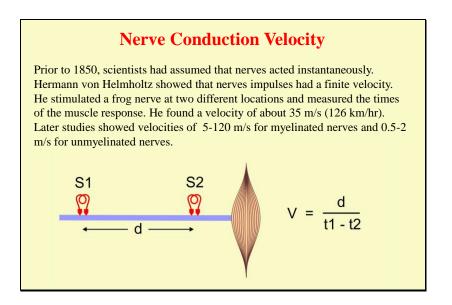


This graph shows how age affects our mental processes.

Any task that requires rapid processing slows down. Tasks requiring access to memory also begin to fail. Performance have been normalized for this graphs. The general rule is that the more complex the task the slower the response.

Knowledge increases slightly with age. We continue to learn and this more than compensates for what we forget. Our vocabulary gets bigger. Our knowledge of the world becomes more extensive.

One thing we can do better as we get older is solve crosswords.



With age the nervous system slows down. So how can we measure the speed of nervous transmission? This slide gives the only mathematical formula in the course. Those of you who hate mathematics can doze off for a minute or two [©]

This is how you measure the velocity of a peripheral nerve. You stimulate the nerve at one location (S1) and record the time of the response in the muscle (t1).

You then stimulate the nerve at a location closer to the muscle (S2) and record the time of its response (t2).

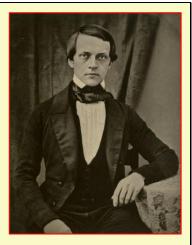
The velocity is then the distance between the two locations (d) divided by the difference in the times.

The fastest human nerve fibers contact at speeds of over 100 m/s - 400 km/hr. Faster than the fastest Ferrari.

The Speed of Thought

Using a similar technique to that for studying the velocity of the nerve impulse in frogs, Helmholtz measured the reaction times to touching the skin at the foot and at the thigh, or at the fingers and at the shoulder. He calculated the human sensory nerve conduction velocity at 60 m/s.

Helmholtz also estimated how long it took for the brain to perceive the stimulus and enact a response. If the subject was highly attentive, this took about 100 ms.



Hermann von Helmholtz, 1848

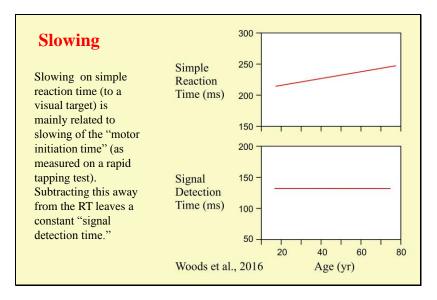
We can use a similar approach to measuring the speed of thought.

The fastest time to press a button following a visual stimulus is about 160 ms (if you are young and really fast O):

30 ms to reach the brain, 100 ms for perceiving the stimulus and initiating the response, 30 ms to go out to the muscles.

The normal average for an adolescent is about 210 ms By the age of 70 years we have slowed to about 250 ms. We lose just under a millisecond a year.

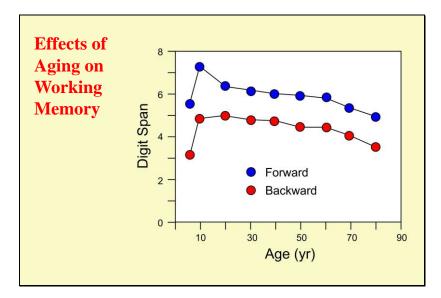
You can try yourself: <u>http://www.humanbenchmark.com/tests/reactiontime</u>



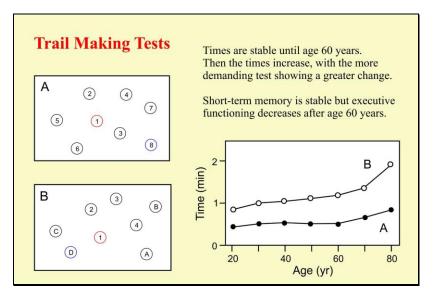
The simplest way to measure the speed of thought is to time the response to a simple stimulus. This slide gives the results of a large study – we slow down by about a half a millisecond per year.

The study also timed how fast we can respond spontaneously and subtracted this away from the reaction time.

There is then no change in the signal detection time.

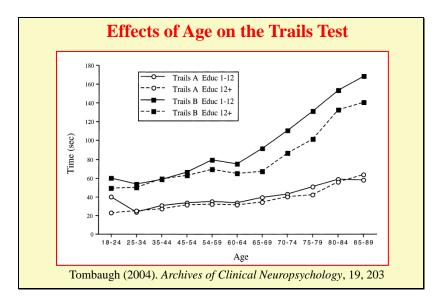


Working memory is not as efficient as we get older. The simplest way to measure this is the digit span – how many numbers can you "keep in mind." Repeat the following numbers "463792." This decreases with age from 20 years onward.



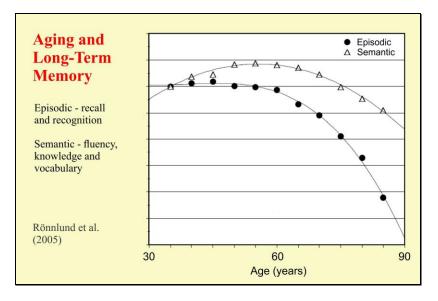
The Trails Tests evaluate the speed of working memory.

Trails A involves linking up the numbers (1 - 2 - 3 ...) scattered on a sheet of paper. It requires finding the next number in the sequence, and drawing a line to connect it to the present number. If you want to do well you should also try to remember where future numbers are on the page. Trails B is more complicated. It requires you to link numbers and letters (-A - 2 - B - 3 ...) The older you are the slower you perform. Happy trails to you!



People who have had more years of education show less effect of aging – at least on the Trails B Test. Somehow education acts to counter the ongoing deterioration that occurs with age. This is the idea of "Cognitive Reserve." Education provides us with more resources to counteract the effect of aging.

We are not sure exactly what this cognitive reserve represents in the brain. More associations between things so that if one is lost others can take over? More learned procedures for processing information? More efficient synapses?

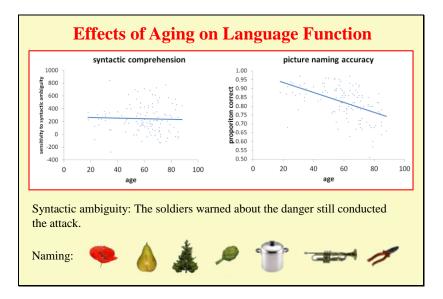


As you get older your performance on tests of episodic memory – remembering lists of words or things that happened – slowly decreases.

You recall fewer words from the list that you memorized. And you recall fewer episodes from your past – what was the name of that movie you saw a month ago?

Semantic knowledge increases with age. You know more words. You do better on crosswords at 70 than you did at 20.

The number of facts that we remember varies with the number we have learned and the number we have forgotten. After age 75 we start to forget more old stuff than we learn new stuff.



Some aspects of language processing decrease with age. Everyone finds it harder to remember the names of people and of things. We may have more words in our brain but it is sometimes

difficult to access them. This becomes clinically significant when we cannot find the names of most of the objects in a picture naming test – then we might have "anomia."

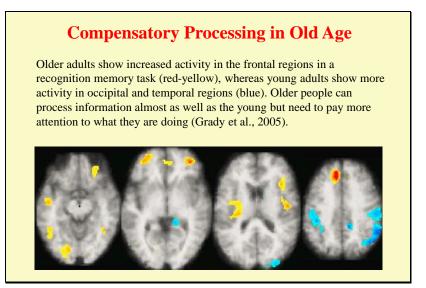
Our use of grammar does not deteriorate. This is tested using syntactically ambivalent sentences. Syntactic ambiguity is evident in "garden-path" sentences such as:

The soldiers warned about the danger still conducted the attack.

Initially we might consider the word "warned" as the main verb of the sentence. Only late do we go back and realize that the soldiers were warned.

A good writer does not compose such sentences. It should be: Although warned about the danger, the soldiers still conducted the attack.

But that does not let us test syntactic comprehension.



A major difficulty with age is that we have to pay more attention. Everything is processed very efficiently in the brains of young subjects and they often can do things without paying much attention. As we get older, incoming information is not as well processed (noisier) and it arrives more slowly. There is less activity in the sensory and memory regions (blue) and we have to pay careful attention in order to get the right answer. This involves the more activity in the frontal regions of the brain (yellow-red).

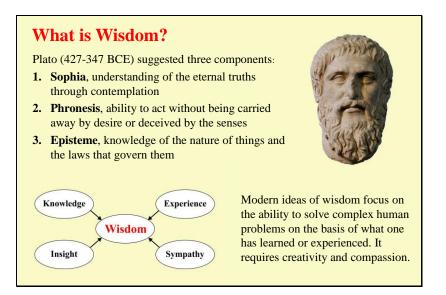


Older people also have difficulty maintaining attention. We get distracted easily.

This video dramatizes the problem of "age-activated attention deficit disorder." The movie shows how distractibility prevents us from accomplishing things, as well as preventing us from laying down memories that can be easily recalled.

The full video is at

https://www.youtube.com/watch?v=6oHBG3ABUJU



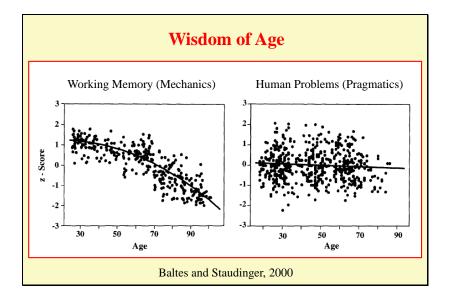
Wisdom is difficult to define and even harder to assess. One person's guru is another person's fool.

Plato described three components to wisdom. Two kinds of knowledge – eternal truths and worldly detail and the ability to act on the basis of this knowledge.

Plato would consider philosophers as the most wise of human beings. Others might consider them too detached from life to be really wise. *Luftmenschen* – those with their heads in the clouds.

Modern concepts of wisdom add the need for creative insight - the ability to generate new answers to old problems.

Important in any concept of wisdom is some idea of morality – compassion/sympathy as a guiding force.



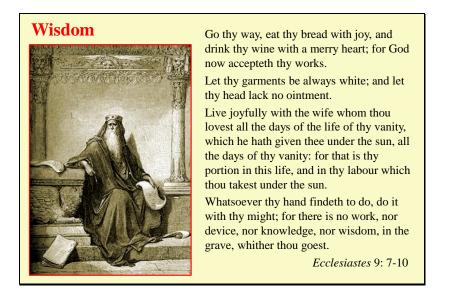
Recent research has measured how well we are able to handle the problems of life – "pragmatics."

This can be assessed by seeing how well subjects propose what to do when confronted with a life problem.

Example: A 15-year-old girl wants to get married right away. What do you advise? Working memory decreases with age but wisdom stays constant.

There is perhaps a problem with how people define wisdom. This study was done by social psychologists and considered how one approached psychosocial problems. The subjects who scored best on the test were social psychologists.

Slide 45



How are we to be wise in our old age?

The Hebrew Bible contains a set of "wisdom books." One of these, once thought to have been written by Solomon but now ascribed to some anonymous preacher is *Ecclesiastes*. He is most famous for the idea that "All is vanity." However, the book also provides some advice on what to do as one grows old.

There are four ideas:

The first is Epicurean – enjoy your life.

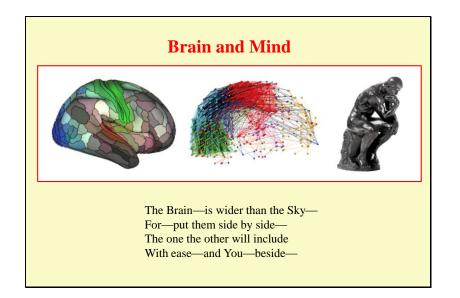
There have been some recent psychological experiments about delayed gratification. Children are left alone with a desirable cookie. They are told that they can eat the cookie now but that if they wait a little while they can eat both this cookie and another one. Children who delay their gratification do better in life.

What Ecclesiastes is saying is that you are no longer a child - You should eat the cookie before you die.

The second is strange – but I wore a white shirt today just in case.

The third is to love one another.

The most important is the last Whatsoever thy hand findeth to do, do it with thy might



We have come to the end of our course.

The brain is a very complex organ. It has multiple specialized areas, each important to processing information in a particular way.

The brain works through the connections between these different areas. The mind is in the interacting networks.

These complex actions allow us to think: to evaluate what has happened in the past, to predict what might happen in the future and to make decisions that are for the best.

Over the past eight weeks, I have probably told you much more than you will remember. Nevertheless, I hope that some of it has made sense and helped you to understand how the brain works.

Eat well, exercise, keep thinking, learn new things, talk to one another – these are the ways to keep the brain healthy. Most important is to keep thinking.



As Emily Dickinson said "The brain is wider than the sky." The conscious brain is as complex as the universe that it tries to comprehend.

The Brain—is wider than the Sky— For—put them side by side— The one the other will include With ease—and You—beside—

The Brain is deeper than the sea— For—hold them—Blue to Blue— The one the other will absorb— As Sponges—Buckets—do—

The Brain is just the weight of God— For—Lift them—Pound for Pound— And they will differ—if they do— As Syllable from Sound—

Emily Dickinson, 1863