Molecular biology of brain and mental disorders

Introduction

SLIDE 1 Human behavior is the product of brain activity, and the brain is the product of two mutually interacting factors: heredity and environment. One important determinant of your individualism is your complement of DNA, which, unless you have an identical twin, is unique. A second factor that makes your brain unique is your history of personal experience. The brain is the organ which is used for the accommodation of the environment and social conditions therefore, it is extremely plastic molded by external influences and experiences. In this lecture we discuss the molecular and cellular processes underlying the pathology of brain and mind disorders. Traditionally, disorders of the brain are treated by neurological and neurosurgical interventions, while the disorders of the mind are treated by psychiatric (pills) and psychological (talk therapy) approaches.

SLIDE 2 The real cause of most of the diseases cannot be directly seen. A symptom, however, is never the disease itself. There are hardly any symptoms that occur in a single disease. There are hardly any symptoms that occur in only a single disease. However, certain symptoms happen together: e.g. chest ache, cough, loss of weigh, fever, asphyxia, and anemia. This group of symptoms was called pectoral disease before 1900. However, there is no pectoral disease, it can be: bronchitis, TBC, asthma, or cancer. Hypothesis and concrete knowledge: we only have hypotheses for many of the diseases; however, we often can cure them without knowing the precise cause.

I. Mental disorders of the mind

SLIDE 3 Psychotherapy. Before the knowledge of brain biology, psychiatry had only theoretical tools for treating mental diseases. The Austrian neurologist psychiatrist Sigmund Freud (1856-1939) had an enormous impact on this field. Freud’s theory of psychoanalysis is based on two major assumptions: (1) that much of mental life is unconscious, and (2) that past experiences, particularly in childhood, shape how a person feels and responds throughout life. According to Freud, mental illness results when the unconscious and conscious elements of psyche come into conflict. The way to resolve the conflict, and to treat the illness, is to help the patient to unearth the hidden secrets of the unconscious. Often, these dark secrets are related to incidents that occurred during childhood and were suppressed from consciousness. Such “psychosocial” approaches to treating mental illness have a sound neurobiological basis. Of course, the “talk therapy” is not appropriate for all mental disorders. However, until recent revolution in biological psychiatry, variations were the only tools available to psychiatrist.

Biological approaches to mental illness. We focus on these approaches in this lecture. We discuss the following issues: anxiety, depression, suicide and schizophrenia.

1. Anxiety

SLIDE 5 Fear is an adaptive response to threatening situations. The inappropriate (or over-exaggerated) expression of fear characterizes anxiety disorders, the most common psychiatric disorders.
Types: (1) generalized anxiety disorders; (2) panic disorders; (3) phobic disorders: agoraphobia (60%); specific phobias (17%); social phobia (8%). The percentages in brackets show the relative occurrence of the disease within the anxiety disorders. Panic disorder: Panic attacks are sudden feeling of intense terror that occur without warning. The symptoms include palpitations, sweating, trembling, shortness of breath, chest pain, nausea, dizziness, tingling sensations, and chills. Most people report an overwhelming fear that they are dying or going crazy and flee from the place where the attacks begins, often seeking emergency medical assistance. Panic disorder is characterized by a persistent worry about further attacks. About 2% of the population suffers from panic disorder, and it is twice as common in women as in men. Agoraphobia (agora = market place) leads to avoidance of situations irrationally perceived as threatening, such as being alone outside home, in a crowd of people, in a car or airplane, or elevator. Generalized anxiety disorder: at least 6 months of persistent and excessive anxiety and worry.

SLIDES 6,7 Molecular biological bases of anxiety disorder The stress response is the coordinated reaction to threatening stimuli. The hypothalamus is centrally involved in orchestrating the appropriate humoral, visceromotor, and somatic motor responses. Let’s focus our attention to the humoral response, which is mediated by the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis regulates the secretion of cortisol (a glucocorticoid) from the adrenal gland in response to stress. Corticotropin-
releasing hormone (CRH) is the chemical messenger between the hypothalamus and the anterior pituitary gland. As a result of CRH (secreted to the blood by neurons of hypothalamus) stimulation, adrenocorticotropic hormone (ACTH) is released by the pituitary gland (in response to CRH,) which in turn travels in the bloodstream to the adrenal gland lying atop the kidney, where it stimulates cortisol release. Cortisol contributes to the body's physiological response to stress. When CRH is overexpressed in transgenic mice, the animals display increased anxiety-like behaviours. When the receptors for CRH are genetically eliminated (knock-out) from mice, they have less anxiety-like behaviour than normal mice. The CRH neurons of the hypothalamus are regulated by two structures: the amygdala and the hippocampus. The amygdala is critical for the fear responses. When the amygdala becomes active, the stress response ensues. Inappropriate activation of the amygdala has been associated with some anxiety disorders. The HPA axis is also regulated by the by the hippocampus. However, hippocampal activation suppresses, rather than stimulates, CRH release. The hippocampus contains numerous glucocorticoid receptors that respond to the cortisol released from the adrenal gland in response to HPA system activation. Thus, the hippocampus normally participates in the negative feedback regulation of the HPA axis, by inhibiting CRH release (and the subsequent release of ACTH and cortisol) when circulating cortisol levels get too high. Continuous exposure to cortisol, such as during periods of chronic stress, can cause hippocampal neurons to die in experimental animals. This degeneration of the hippocampus may set off a vicious cycle, in which the stress response becomes more pronounced, leading to even greater cortisol release and more hippocampal damage. Anxiety disorders have been related to both hyperactivity of the amygdala and diminished activity of the hippocampus. The amygdala and the hippocampus both receive highly processed information from the prefrontal cortex. This region is involved with personality, planning, inhibition of behaviors, abstract thinking, emotion, and short-term memory. To function efficiently, the prefrontal cortex requires signaling by neurotransmitters such as dopamine and norepinephrine. Catechol-O-methyltransferase helps maintain appropriate levels of these neurotransmitters in this part of the brain.

Treatments of anxiety disorder

**SLIDE 8 Psychotherapy**: There is a strong learning component of fear. The therapist gradually increases the exposure of the patient to the stimuli that produce anxiety, reinforcing the notion that the stimuli are not dangerous. At the neurobiological level, the aim of the psychotherapy is to alter the connections in the brain such that the real or imagined stimuli no longer evoke the stress response.

Anxiolytic medications: The major classes of anxiolytic drugs currently used in the treatment of anxiety disorders are the benzodiazepines and serotonin-selective reuptake inhibitors (the latter one will be discussed at the topic of depression). GABA<sub>A</sub> receptors are GABA-gated ion channels that mediate last IPSPs (inhibitory post-synaptic potentials). In addition to its GABA binding site, the GABA<sub>A</sub> receptor contains site where chemicals can act to powerfully modulate channel function. Benzodiazepines bind to one of these sites and act to make GABA much more effective in opening the channel and producing inhibition. The site on the receptor that binds benzodiazepines is believed to be used normally by a naturally occurring brain chemical, although the identity of this endogenous molecule has not been established. Virtually, all drugs that stimulate GABA actions are anxiolytic, including ethanol (the binding site for ethanol is not shown on the picture). Reduction in anxiety is likely to explain, at least in part, the widespread social use of alcohol. This anxiolytic effects of alcohol are an obvious reason that anxiety disorders and alcohol abuse often go hand-in-hand. Serotonin-selective reuptake inhibitors (SSRIs) are also utilized as anxiolytic drugs, but this topic will be discussed in the topic of depression.

Genetic bases of anxiety disorder A genetic predisposition has been established for many anxiety disorders, although we know very little about the genetic background of this disease. **The worry gene** (COMT gene) Scientists aren’t doing much better at understanding the biological role of another player in the dopamine circuit. Dozens of studies have tried to figure out the gene for catechol O-methyltransferase (COMT), an enzyme that breaks down dopamine in the prefrontal cortex, the seat of
higher cognitive functions such as planning and reasoning. The two major variants of the gene code for enzymes that differ by one amino acid: The substitution of a valine for a methionine revs up the protein’s activity fourfold. Both the high- and low-activity versions of the gene have their costs and benefits. Mice with the high-activity COMT – meaningless dopamine in the synapses - have poor memories and reduced sensitivity to pain. With the gene knocked out, and thus higher dopamine activity, mice show increased startle and anxiety responses. In humans as well, different versions of the gene have been implicated in cognitive and emotional dysfunction.

In several studies, people with two low activity COMT genes have tested high for fear, anxiety, and negative thinking. A study at Yale University in 2005, for example, gave 497 undergraduates personality tests and found that those with low activity COMT genes were more neurotic and less extraverted. In research getting closer to the interface between biology and behavior, researchers reported a difference in a simple test that has come to be recognized as a reliable indicator for anxiety: the startle reflex, as manifested in involuntary eye blinking in response to a sudden noise or unpleasant pictures. Among 96 female psychology students, individuals with two copies of the low activity COMT had the most exaggerated startle responses. Brain-imaging studies of 100 normal adults found that those with the low-activity COMT have denser nerve connections. The elevated dopamine in the prefrontal cortex may bolster temporary connections, leading to better concentration but reduced ability to shift focus and more behavioral rigidity. As a result, a person may dwell excessively on stressful thoughts. So the gene seems to come with a tradeoff - better cognitive function but more anxiety. The trouble with a lot of research on COMT, however, is that some studies find significant linkages only in women and others don’t find any at all.

2. Depression

SLIDE 9 Depression is a serious disease. It is the leading cause of disability, and also the leading contributor to suicide world-wide, which claims about one million lives each year all over the world. The major depression (a severe form of depression) is unipolar and affects 5% of the population. Bipolar disorder consists of a repeated episodes of mania, or mixed episodes of mania and depression, and therefore is also called manic-depressive disorder.

SLIDES 10 The monoamine hypothesis (1) A drug called reserpin, introduced to control high blood pressure, caused psychotic depression in about 20% of cases. Reserpin depletes central catecholamines and serotonin by interfering with their loading into synaptic vesicles. (2) Another class of drugs (isonicid) introduced to treat tuberculosis caused a marked elevation in mood. These drugs inhibit monoamine oxidase (MAO), the enzyme that destroys catecholamines and serotonin. (3) Another piece of the puzzle fell into place when neuroscientists recognized that the drug imipramin, introduced some years earlier as an antidepressant, inhibits the reuptake of released serotonin and norepinephrine, thus promoting their action in the synaptic cleft. As a result of this observations, researchers developed the hypothesis that mood is closely tied to the levels of released monoamine neurotransmitters in the brain. According to this idea, called monoamine hypothesis of mood disorders, depression is a consequence of a deficit in one of these diffuse modulatory systems. The shortages of monoamine hypothesis. Indeed, many of the modern drug treatments for depression have in common enhanced neurotransmission at central serotonergic and/or noradrenergic synapses. A direct correlation between mood and modulator, however, is too simplistic. Perhaps the most striking problem is the clinical finding that the antidepressant action of all of these drugs takes several weeks to develop, even though they have almost immediate effects on transmission at the modulatory synapses. Another concern is that other drugs that raise norepinephrine levels in the synaptic clefts, like cocaine, are not effective as antidepressants.

SLIDE 11 The diathesis - stress hypothesis The diathesis (genetic predisposition) – stress model is a psychological hypothesis that explains behavior as both a result of biological and genetic factors (“nature”), and life experiences (“nurture”). This model thus assumes that a disposition towards a certain disorder may result from a combination of one’s genetics and early learning. According to the model, this predisposition, in combination with certain kinds of environmental stress, results in abnormal behavior.
This hypothesis is often used to describe the pronunciation of mental disorders, like depression or schizophrenia that are produced by the interaction of a vulnerable hereditary predisposition, with precipitating events in the environment. According to the diathesis-stress hypothesis of mood disorders, the HPA axis is the main site where genetic and environmental influences converge to cause mood disorders. One of the most robust findings in all biological psychiatry is hyperactivity in of the HPA system in severely depressed patients: blood cortisol levels are elevated, as is the concentration of CRH in the cerebrospinal fluid. Animal studies are highly suggestive. Injected CRH into the brains of animals produces behavioral effects similar to those of major depression. Recall that activation of the hippocampal glucocorticoid receptor by cortisol normally leads to feedback inhibition of the HPA axis. In depressed patients, this negative feedback is disrupted, explaining why HPA function is hyperactive. A molecular basis for the diminished hippocampal response to cortisol is a decreased number of glucocorticoid receptors (plus cell death). What regulates glucocorticoid receptor number? In a fascinating parallel with the factors implicated in mood disorders, the answer is (1) genes, (2) monoamines and (2) early childhood experience. In rats, it has been shown that the amount of glucocorticoid receptor gene expression is regulated by early sensory experience. Rats that received a lot of maternal care as pups express more glucocorticoid receptors in their hippocampus, less CRH in their hypothalamus, and reduced anxiety as adults. Tactile stimulation activates the ascending serotonergic inputs to hippocampus, and the serotonin triggers a long-lasting increase in the expression of the glucocorticoid receptor gene. However, the beneficial effect of experience is restricted to a critical period of early postnatal life. Childhood abuse and neglect, in addition to genetic factors factors, are known to put people at risk for developing mood disorders.

**Treatment:** see SLIDES 2-16

**Electroconvulsive therapy** No-one is certain how ECT works, and there are a number of theories. It is thought that ECT causes the release of neurotransmitters and, probably more importantly, makes the neurotransmitters more likely to work and so help recovery. Recent research has suggested that ECT can stimulate the growth of new blood vessels in certain areas of the brain.

**Psychotherapy** see above for details (SLIDE 3) A new approach: Cognitive Behavioral Therapy can help you to change how you think ("Cognitive") and what you do ("Behaviour"). Unlike some of the other talking treatments, it focuses on the "here and now" problems and difficulties. Instead of focusing on the causes of your distress or symptoms in the past, it looks for ways to improve your state of mind now.

**Antidepresants**

**Tricyclic antidepressants (TCAs)** are named after their chemical structure, which contains three rings of atoms. The tetracyclic antidepressants (TeCAs), which contain four rings of atoms, are a closely related group of antidepressant compounds. In recent times, the TCAs have been largely replaced in clinical use in most parts of the world by newer antidepressants such as the selective serotonin reuptake inhibitors (SSRIs), though they are still sometimes prescribes for certain.

**Selective serotonin reuptake inhibitors (SSRIs)** Precisely how SSRIs affect depression isn't clear. Certain brain chemicals called neurotransmitters are associated with depression, including the neurotransmitter serotonin. Some research suggests that abnormalities in neurotransmitter activity affect mood and behavior. SSRIs seem to relieve symptoms of depression by blocking the reabsorption (reuptake) of serotonin by certain nerve cells in the brain. This leaves more serotonin available in the brain. Increased serotonin enhances neurotransmission — the sending of nerve impulses — and improves mood. SSRIs are called selective because they seem to affect only serotonin, not other neurotransmitters. Antidepressants, in general, may also work by playing a neuroprotective role in how they relieve anxiety and depression. It’s thought that antidepressants may increase the effects of brain receptors that help nerve cells keep sensitivity to glutamate neurotransmitters in check. This increased support of nerve cells lowers
glutamate sensitivity, providing protection against the glutamate overwhelming and exciting key brain areas related to anxiety and depression.

**MAO inhibitors (MAOIs)** act by inhibiting the activity of monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitter and thereby increasing their availability. The early MAOIs inhibited monoamine oxidase irreversibly. When they react with monoamine oxidase, they permanently deactivate it, and the enzyme cannot function until it has been replaced by the body, which can take about two weeks.

**Genetic Factors** The rates of illness in relatives are higher than occur in general population. About 20 percent of the parents of patients with affective illness also have affective disorders, the rate in brothers and sisters and children is even higher - possibly as high as 30 percent. The rate tends to be higher in the female relatives. For identical twins the rate is around 50 - 60 percent. For the role of SERT gene in depression, see the lecture Human, Society and Environment.

**The gene of depression (SERT gene)** Some people are like Woody Allen characters who melt down in the face of the smallest obstacles. Others seem to have a thick hide against life’s slings and arrows. The roots of such resilience may lie in a gene for a protein that regulates serotonin, a brain messenger that has been associated with emotional ups and downs. The gene is called *SERT* for serotonin transporter. It has been reported that the length of the regulatory DNA at the beginning of *SERT* affected human behavior. A research team found that among 505 adults, those scoring high on various tests measuring “neuroticism” - depression and anxiety - tended to have one or two copies of a short variant whereas those who were more laid back had only the long form. The short version translates into more serotonin in the synapse, and too much serotonin leads to anxiety, in both animals and humans. The short version accounted for up to 4% of the increase in anxiety and negative emotions in this group. Four percent doesn’t sound like much, but it’s huge for any personality trait. In fact, scientists have been able to find “no gene in the intervening years that has accounted for that much variability. In another landmark study researchers showed that the effect of the gene depends on life experiences. In New Zealand, researchers tracked 847 people over more than 20 years from the age of 3. The researchers counted stressful life events occurring between the ages of 21 and 26 and asked subjects if they had been depressed in the past year. Among people who had not reported any major life stresses, the probability of depression was low regardless of their *SERT* alleles. But among people who had been through four or more stressful experiences, 43% of those with two short alleles reported a major depressive episode - more than double the proportion of subjects with two long alleles. The study also showed that almost two-thirds of people with a history of abuse as children experienced major depression as adults if they had two short alleles. But child abuse didn’t raise the risk of adult depression in people with two long alleles. Unfortunately, however, the picture is still unclear. Other investigators argue that the published studies weren’t based on large enough samples and that the interaction effect between the gene and stressful life events is probably negligible. The more researchers look into this gene, the more widespread its associations appear to be, adding to the confusion. The serotonin transporter is implicated in everything from heart disease to sleep disorders and irritable bowel syndrome [as well as] schizophrenia, depression, attention deficit hyperactivity disorder, autism, and sensation seeking, to name just a few. With such a broad scope, its effects on behavior must be extremely general. So to call it a resilience gene doesn’t really fit.

**3. Schizophrenia**

**SLIDE 17** Schizophrenia is characterized by a loss of contact with reality, and disruption of thought, perception, mood, and movement. It is still not clear whether what is called schizophrenia is a single disease or several. According to current diagnostic criteria, schizophrenia is classified into a number of types, paranoid, disorganized and catatonic schizophrenia.

**Biological basis of schizophrenia** Schizophrenia runs in families. If you identical twin has schizophrenia, the probability is about 50% that you will also have it. The chances you will have the disease decline as the number of genes you share with an
affected family member decreases. These findings argue that schizophrenia is a genetic disease. Recently, researchers have identified several specific genes that seem to increase susceptibility to schizophrenia. Nearly all of these genes have important roles in synaptic transmission, its plasticity, or the growth of synapses. Why in 50% of cases, is one sibling spared when the other has schizophrenia? The answer must lie in the environment. In other words, faulty genes seem to make some people vulnerable to environmental factors that cause schizophrenia. Although the symptoms may not appear until a person reaches his twenties, considerable evidence indicates that the biological changes causing the condition begin early in development, perhaps prenatally. The brains of schizophrenics have a significantly larger ventricle-to-brain size ratio than people who do not have the disorder. Important physical changes in their brains also occur in the microscopic structure and function of cortical connections. For example, schizophrenics often have deficits in the myelin sheaths surrounding axons in their cerebral cortex, although it is not clear whether this is a cause or consequence of the disease. Changes in synapses and several neurotransmitter systems have also been implicated in schizophrenia. Particular attention has focused on alterations in chemical synaptic transmission mediated by dopamine and glutamate.

The cause(s) of schizophrenia: It has been argued that schizophrenia may be the evolutionary price we pay for a left brain hemisphere specialization for language. Since psychosis is associated with greater levels of right brain hemisphere activation and a reduction in the usual left brain hemisphere dominance, our language abilities may have evolved at the cost of causing schizophrenia when this system breaks down.

SLIDES 18-19 The dopamine hypothesis claims that schizophrenia is caused by dopamine hyperactivity in the brain centers controlling behavior. A link between mesocorticolimbic dopamine system and schizophrenia has been made on the basis of two major observations. (a) The first relates to the hallucinogenic effects of amphetamine (a psychostimulant drug) in otherwise healthy people. Amphetamine causes the increase of dopamine in the cytosol of the presynaptic dopaminergic neurons. It is not known whether the elevated dopamine level is caused by the inhibitory effect of the amphetamine on the dopamine transporter (reuptake pump), or this drug acts at the vesicular level. This suggests that psychosis is somehow related to too much dopamine in the brain. (b) A second reason to associate dopamine with schizophrenia relates to the observation that neuroleptic (antipsychotic) drugs have been found to be potent blockers of dopamine receptors, specifically D2 receptors. Together, according to the dopamine hypothesis of schizophrenia, psychotic episodes in schizophrenia are triggered specifically by the activation of dopamine receptors.

SLIDE 20 The glutamate hypothesis claims that the influence of frontal lobe (mediated by glutamatergic neurons) over the brain centers controlling behavior, decreases, which results overexpression of the dopamin in these centers. (1) An indication that there is more to schizophrenia than dopamine comes from the behavioral effect of phencyclidine (PCP). The drug was introduced in the 1950s as an anesthetic. Trials in human were a failure, however, because many patients experienced adverse postoperative side effects, sometimes lasting for days, they included hallucinations and paranoia. Tragically, PCP is now a common illegal drug that is abused; it is known as “angel dust” or “hog”. PCP has no effect on the dopaminergic transmission. PCP acts by inhibiting NMDA receptors (a subtype of glutamate receptor). Thus, according to the glutamate hypothesis of schizophrenia, the disease reflects diminished activation of NMDA receptors in the brain. (2) A further evidence for the glutamate hypothesis is that the he majority of the genes that have recently been associated with an increased risk for schizophrenia can influence the function of modulatory sites on the NMDA receptor or intracellular-receptor interacting proteins that link glutamate receptors to signal transduction pathways

Treatment The first generation of antipsychotics - termed conventional or 'typical' antipsychotics, inhibit dopamine D2 receptors and are moderately effective in treating positive symptoms of schizophrenia (for example, hallucinations), but may cause extrapyramidal movement disorders. Second-generation 'atypical' antipsychotics inhibit D2 receptors in conjunction with other receptors (notably 5-HT₂A, a serotonin receptor). Medication ceases only the symptoms of schizophrenia but not the disease itself. SLIDE 21 In September 2007, Eli Lilly announced results of a 4-week Phase II trial of their metabotropic glutamate receptor 2/3 (mGluR2/3) agonist LY2140023 for schizophrenia. The mechanisms by which mGluR agonists can alleviate schizophrenia remains unclear. Group 1 mGluRs (mGluR1 and 5) are located post-synaptically, peripheral to the post-synaptic density where they may regulate both glutamatergic and dopaminergic signaling. Group 2 mGluRs (mGluR2 and 3) are found pre-synaptically, directly modulating glutamate release. In addition, these receptors can be found in glia.

BASIC REQUIREMENTS
4. Suicide

SLIDE 22  The first evidence of serotonergic system alterations in the brain of suicide attempters emerged when American investigators demonstrated decreased levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin (5-HT), in the cerebrospinal fluid (CSF) of a substantial subgroup of suicide attempters. For the last quarter century, elucidation of the neurotransmitter circuits and receptors disordered in both the pathophysiology of depression and suicide has been the subject of intense study. This research has accrued substantial evidence to suggest that the serotonergic system is altered in both depressed patients and suicide victims. One of the seminal, and as yet unresolved, issues in the field is whether the biology of suicide is distinct from the biology of depression. Although there may well be some overlap, there is growing evidence of a distinct biology of suicide. The abundance of evidence suggesting that the serotonergic system is altered in suicidal behavior has prompted investigators to scrutinize the potential role of the serotonin transporter (SERT) in the pathophysiology of suicide. The SERT is believed to be primarily responsible for the termination of action of 5-HT after it is released from the nerve terminal into the synapse. It is located on the presynaptic neuron and takes up one 5-HT molecule concurrently with one Na+ ion, decreasing extracellular fluid concentrations of 5-HT to levels where postsynaptic receptor activation ceases.

II. Disorders of the brain

5. Prion disease

SLIDES 23, 24

Types: 1. Human prion diseases: Creutzfeld-Jakob disease (CJD), vCJD (variant CJD), kuru
2. Animal prion diseases bovine spongiform encephalitis (BSE, mad cow), scrapie

(1) Sporadic” means “occurring occasionally or unpredictably”. No obvious risk factors have been discovered for sporadic CJD. (2) Familial (inherited) prion diseases mean that the disease is caused directly by genetic abnormalities in the gene, PRNP that encodes the prion protein. (3) Acquired prion diseases: infection

Prion diseases belong to group of progressive conditions that affect the nervous system in humans and animals. The signs and symptoms of these conditions typically begin in adulthood, and these disorders lead to death within a few months to several years. Only a small percentage of prion disease cases run in families (e.g. classic CJD). Most cases are sporadic, which means they occur in people without any known risk factors or gene mutations: e.g., the classic Creutzfeldt-Jakob disease (CJD). Rarely, prion diseases can be transmitted by accidental exposure to prion-contaminated tissues during a medical procedure. One type of prion disease in humans, variant Creutzfeldt-Jakob disease (vCJD), is acquired by eating beef products obtained from cattle with prion disease. In cows, this form of the disease is known as bovine spongiform encephalopathy (BSE) or, more commonly, “mad cow” disease. Another example of an acquired human prion disease is kuru, which was identified in the South Fore tribe in Papua New Guinea. The disorder was transmitted when tribe members ate the tissue of affected people during cannibalistic funeral rituals. The familial forms of prion diseases are caused by inherited mutations in the prion gene (PRNP). Normally, prion protein (PrP) protein is likely involved in transporting copper into cells. It may also play a role in protecting brain cells and helping them communicate. In familial cases of prion disease, mutations in the PRNP gene cause cells to produce an abnormal form of the prion protein known as PrPSc. In iatrogenic and acquired cases, an affected person develops prion disease from exposure to this abnormal protein. In a process that is not fully understood, PrPSc has the ability to convert the normal prion protein, PrPSc into more PrPSc. This abnormal protein builds up in the brain, forming clumps that damage or destroy nerve cells. The loss of these cells creates microscopic sponge-like holes in the brain, which leads to the signs and symptoms of prion disease.

6a. Trinucleotide repeat disorders

SLIDE 25  Trinucleotide repeat disorders are due to stretches of DNA in a gene that contain the same trinucleotide sequence repeated many times. These repeats are a subset of unstable microsatellite repeats that occur throughout all genomic sequences. If the repeat is present in a gene, an expansion of the repeat results in a defective gene product and often disease. At present there are 14 documented trinucleotide repeat disorders that affect humans (seven of them can be seen on the slide. Do not study them!). Eight of these disorders have the same repeated codon, CAG, that codes for glutamine (Q). These diseases are commonly referred to as polyglutamine (or PolyQ) diseases. The other six disorders do not have similar repeats and are classified as non-polyglutamine diseases. A common symptom of PolyQ diseases is characterized by a progressive degeneration of nerve cells usually affecting people later in life. Although these diseases share the same repeated codon (CAG = glutamine) and some symptoms, the repeats for the different polyglutamine diseases occur on different chromosomes. The non-PolyQ diseases do not share any specific symptoms and are unlike the PolyQ diseases. Trinucleotide repeat disorders generally show genetic anticipations, where their severity increases with each successive generation that inherits them. Trinucleotide repeat disorders are the result of extensive duplication of a single codon. In fact, the cause is trinucleotide expansion up to a repeat number above a certain threshold level.
6b. Huntington's disease

SLIDES 26, 27 Huntington's disease (HD) results from genetically programmed degeneration of nerve cells in certain areas of the brain.

**Genetic background:** The HD gene on chromosome 4 contains 67 exons. HD is part of a group of disorders that arise from a specific genetic mutation called guanine expansion. Huntington's disease arises from a mutated version of the huntingtin gene that carries an extra DNA segment that repeats the CAG triplet (encoding glutamine) many times over. DNA expansion is normal to a certain extent; healthy people may have anywhere from 6 and 20 repeats in a gene, but a person with HD has 40 to 80 repeats or more. Triplet expansion is caused by slippage during DNA replication. Due to the repetitive nature of the DNA sequence in these regions 'loop out' structures may form during DNA replication while maintaining complementary base paring between the parent strand and daughter strand being synthesized. If the loop out structure is formed from sequence on the daughter strand this will result in an increase in the number of repeats. However if the loop out structure is formed on the parent strand a decrease in the number of repeats occurs. It appears that expansion of these repeats is more common that reduction. HD prevalence, per country, is up to 7 people in 100,000 (in populations of Western European inheritance), but can be much higher in localized regions. Huntington's disease is inherited autosomal dominantly, meaning that an affected individual typically inherits a copy of the gene with an expanded trinucleotide repeat (the mutant allele) from an affected parent. HD generally occurs later in life, but the number of CAG repeats vary among affected people. The greater the number of repeats, the earlier in life symptoms appear.

**Affected brain regions:** Specifically affected are cells of the basal ganglia, structures deep within the brain that have many important functions, including coordinating movement. Also affected is the cortex, which controls thought, perception, and memory. Total brain weight may be reduced by as much as 25–30% in people who have advanced cases of HD. The huntingtin (HTT) is expressed in all mammalian cells (including human), but the highest concentrations are found in the brain and testes. The function of HTT in humans is unclear: proteins it interacts with are involved in transcription, cell signaling and intracellular transporting. It is currently concluded that the disease is not caused by inadequate production of HTT, but by a gain of toxic function of (mutant) mHTT.

**Cellular changes due to mHTT:** During posttranslational modification of mutant HTT (mHTT), cleavage of the protein can leave behind shorter fragments constituted of parts of the polyglutamine expansion. These fragments can then misfold and coalesce, in a process called protein aggregation, to form inclusion bodies within cells. Inclusion bodies have been found in both the nucleus and the cytoplasm of the cell. Inclusion bodies in cells of the brain are one of the earliest pathological changes, and some experiments have found that they can be toxic for the cell, but other experiments have shown that they may form as part of the bodies defense mechanism and help protect cells, so their causal role in HD is still in debate. The influence of the protein fragments or the resultant inclusions on biological functions are the likeliest cause of cell death and HD pathology. The exact manner in which these causes cell death has not been isolated, but several possible pathways have been identified, and it is possible that neurotoxicity may be caused by a combination of these. Possible pathways that have been shown to cause cell death in experiments include the effects on chaperone proteins, which help fold proteins and remove misfolded ones; interactions with caspases which play a role in the process of apoptosis; impairment of energy production within cells; and effects on the expression of genes.

7. ALS

**(Amyotrophic Lateral Sclerosis)**

SLIDE 28 ALS is one of the most common neuromuscular diseases worldwide, and people of all races and ethnic backgrounds are affected. One to 2 people per 100,000 develop ALS each year. ALS a form of motoneuron disease is a progressive, fatal, neurodegenerative disease caused by the degeneration and death of motor neurons, the nerve cells in the spinal cord and brain that control voluntary muscle movement. The disorder causes muscle weakness and atrophy throughout
the body. Unable to function, the muscles gradually weaken and eventually atrophy because of that denervation. The cause of ALS is not known, though an important step toward answering that question came in 1993 when scientists discovered that mutations in the gene that produces the Cu/Zn superoxide dismutase (SOD1) enzyme were associated with some cases (approximately 20%) of familial ALS. This enzyme is a powerful antioxidant that protects the body from damage caused by superoxide, a toxic free radical. Free radicals can accumulate and cause damage to DNA and proteins within cells. Although it is not yet clear how the SOD1 gene mutation leads to motor neuron degeneration, researchers have theorized that an accumulation of free radicals may result from the faulty functioning of this gene. Current research, however, indicates that motor neuron death is not likely a result of lost or compromised dismutase activity, suggesting mutant SOD1 induces toxicity in some other way (a gain of function). In addition, aggregation of proteins has been found to be a common pathological feature of both familial and sporadic ALS. It is speculated that aggregate accumulation of mutant SOD1 plays a role in disrupting cellular functions by damaging mitochondria, proteasomes, and chaperones, which eventually can lead to apoptosis. No cure has yet been found.

8. Parkinson’s disease

SLIDE 29 The dopamine hypothesis Parkinson's disease is a degenerative disease of the brain that often impairs motor skills, speech, and other functions. Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement and, in extreme cases, a loss of physical movement. The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. This is the dopamine hypothesis of Parkinson's disease.

SLIDE 30 Dopaminergic pathways of the human brain in normal condition (left) and Parkinson's disease (right). Red Arrows indicate suppression of the target, blue arrows indicate stimulation of target structure. The symptoms of Parkinson's disease result from the loss of dopamine-secreting (dopaminergic) cells of the substantia nigra. These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway. The direct pathway facilitates movement and the indirect pathway inhibits movement, thus the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in increased inhibition of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia. There are four major dopamine pathways in the brain; the nigrostriatal pathway (substantia nigra → basal ganglia), referred to above, mediates movement and is the most conspicuously affected in early Parkinson's disease. Disruption of dopamine along the non-striatal pathways likely explains much of the neuropsychiatric pathology associated with Parkinson's disease.

The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha synuclein bound to ubiquitin in the damaged cells. The alpha synuclein-ubiquitin complex cannot be directed to the proteosome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. The latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles; the endoplasmic reticulum (ER) and the Golgi apparatus. Excessive accumulations of iron, which are toxic to nerve cells, are also typically observed in conjunction with the protein inclusions. The most likely mechanism is generation of reactive oxygen species. Iron also induces aggregation of synuclein by oxidative mechanisms. The precise mechanism whereby such aggregates of alpha-synuclein damage the cells is not known.

SLIDE 31 Treatment At present, there is no cure for PD, but medications or surgery can provide relief from the symptoms. The most widely used form of treatment is (1) L-dopa in various forms. L-dopa is transformed into dopamine in the dopaminergic neurons by dopa-decarboxylase. However, only 1-5% of L-dopa enters the dopaminergic neurons. The remaining L-dopa is often metabolized to dopamine elsewhere, causing a wide variety of side effects. Due to feedback inhibition, L-dopa results in a reduction in the endogenous formation of L-dopa, and so eventually becomes counterproductive. (2) COMT inhibitors inhibit COMT enzyme (located in the post-synaptic membrane and degrades monoamines in the synaptic cleft),
thereby prolonging dopamine effect. It is used in combination with L-dopa administration. Not too effective therapy. (3) The dopamine agonists are moderately effective. These have their own side effects including those listed above in addition to somnolence, hallucinations and/or insomnia. Several forms of dopamine agonism have been linked with a markedly increased risk of problem gambling. Dopamine agonists initially act by stimulating some of the dopamine receptors. However, they cause the dopamine receptors to become progressively less sensitive, thereby eventually increasing the symptoms. (4) MAO-B inhibitors reduce the symptoms by inhibiting monoamine oxidase-B (MAO-B), thereby inhibiting the breakdown of dopamine secreted by the dopaminergic neurons.

SLIDE 32 Currently under investigation of alternative therapies including gene therapy, cell replacement therapy and electrode implantation. (1) This involves using a non-infectious virus to shuttle a gene into a part of the brain called the subthalamic nucleus (STN). The gene used leads to the production of an enzyme called glutamic acid decarboxylase (GAD), which catalyses the production of a neurotransmitter called GABA. GABA acts as a direct inhibitor on the overactive cells in the STN. Another approach is the delivery of tyrosine hydroxylase gene to substantia nigra by means of viral vectors. (2) Implantation of stem cells genetically engineered to produce dopamine or stem cells that transform into dopamine-producing cells has already started being used. These could not constitute cures because they do not address the considerable loss of activity of the dopaminergic neurons. Initial results have been unsatisfactory, with patients still retaining their drugs and symptoms. (3) An established treatment for Parkinson's disease involves implanting electrodes in the brain (to nucleus subthalamicus and globus pallidus) and connecting them to a pacemaker (DBS: deep brain stimulation).

9. Alzheimer’s disease

SLIDES 33, 34 The most noticeable deficit of Alzheimer’s disease (AD) is memory loss, which shows up as difficulty in remembering recently learned facts and inability to acquire new information. Subtle problems with the executive functions of attentiveness, planning flexibility and abstract thinking or impairments in semantic memory (memory of meanings), can also be symptomatic of the early stages of AD. Apathy can be observed at this stage, and remains the most persistent neuropsychiatric symptom throughout the course of the disease.

Causes Typical microscopy image shows neurofibrillary tangles and amyloid plaques in the diseased tissues. Three major competing hypotheses exist to explain the cause of the disease. (1) The oldest, on which most currently available drug therapies are based, is the cholinergic hypothesis, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. (2) The amyloid hypothesis postulates that amyloid beta (Aß) deposits are the fundamental cause of the disease. It is a compelling theory because the gene for the amyloid beta precursor protein (APP) is located on chromosome 21, and people with trisomy 21 (Down Syndrome) who thus have an extra gene copy almost universally exhibit AD by 40 years of age. Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits. Deposition of amyloid plaques does not correlate well with neuron loss. (3) This observation supports the tau hypothesis, the idea that tau protein abnormalities initiate the disease cascade. In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies. When this occurs, the microtubules disintegrate, collapsing the neuron's transport system.

Less than 10% of AD cases occurring before 60 years of age are due to autosomal dominant mutations, which therefore represent less than 0.01% of all cases. These mutations have been discovered in three different genes: amyloid precursor protein (APP) and presenilin 1 and 2. Most mutations in the APP and presenilin genes increase the production of a small protein called Abeta42, which is the main component of senile plaques. Most cases of Alzheimer's disease do not exhibit familial inheritance, but genes may act as risk factors. The best known genetic risk factor is the inheritance of the ε4 allele of the apolipoprotein E (APOE). This gene is implicated in up to 50% of late-onset sporadic Alzheimer's cases. Geneticists agree that numerous other genes also act as risk factors or have protective effects that influence the development of late onset AD. Over 400 genes have been tested for association with late-onset sporadic AD. There is no cure for Alzheimer's disease; available treatments offer relatively small symptomatic benefit but remain palliative in nature.
**Videos**

**Huntington**  [http://www.dailymotion.com/video/x1j0j5_huntingtons-disease_family](http://www.dailymotion.com/video/x1j0j5_huntingtons-disease_family)

**Parkinson**  [http://video.about.com/seniorhealth/Parkinson-s-Disease.htm](http://video.about.com/seniorhealth/Parkinson-s-Disease.htm)


**Alzheimer**

[http://www.youtube.com/watch?v=9Wv9jrkgXc](http://www.youtube.com/watch?v=9Wv9jrkgXc)

[http://www.youtube.com/watch?v=IcuDz7tOL7E](http://www.youtube.com/watch?v=IcuDz7tOL7E)

[http://www.youtube.com/watch?v=1aXINAiMCPg&feature=related](http://www.youtube.com/watch?v=1aXINAiMCPg&feature=related)

[http://www.youtube.com/watch?v=r9qeYjMor0I&feature=PlayList&p=69CEC699C8BDCC5C&index=2](http://www.youtube.com/watch?v=r9qeYjMor0I&feature=PlayList&p=69CEC699C8BDCC5C&index=2)