Dopamine and SCIO technology

Dopamine is a neurotransmitter. It is a chemical messenger that helps in the transmission of signals in the brain and other vital areas. Dopamine is found in humans as well as animals, including both vertebrates and invertebrates.

Dopamine is commonly known as a chemical produced by the brain that relates to the sensation of pleasure. Dopamine regulates virtually all bodily functions, including eye movement, heartbeat and breathing. Various types of dopamine (there are several) must exist in carefully regulated amounts in order for these functions to be properly controlled.

With too little dopamine movement becomes difficult. Parkinson's disease is one result of low levels of dopamine. Too much dopamine results in hyperactivity and an inability to remain still. The most extreme form of this is tardive dyskinesia.

Brain Regions Affected by Parkinson’s Disease

Parkinson’s disease
We Can't Stop the Dopamine

Author Louann Brizendine, M.D., says:

Researchers at Stanford University showed that playing Wii activates parts of the male brain linked to dopamine production. Boys get rewarded by this feel-good brain chemical, just as they do when roughhousing. The more opponents they conquer, the more stimulated their male brain becomes, and the more dopamine their brains release. It's a thrill a minute.

**Dopamine levels in a normal and a Parkinson's affected neuron.**

Normal Neuron

- Normal movement

Parkinson's affected Neuron

- Movement disorders

**Professor X of the X-Men uses GSRtDCs to increase his mental ability.**

**Why don't you??**

**Normal Brain**

**ADHD**

**After 1 GSRtDCs**

**After 3 sessions**

**After 5 sessions**

**Normal Brain map**

**severe ADHD**

**1 Eductor session**

**3 GSRtDCs**

**5 GSRtDCs**
Dopamine Measurement during Prolonged Deep Brain Stimulation: A Proof-of-Principle Study of Paired Pulse Voltammetry

Seungleal Brian Park, Emily Jane Knight, Su-Youne Chang, J. Luis Lujan, Dong Pyo Jang, Kevin E. Bennet and Kendall H. Lee

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Abstract
Purpose Deep Brain Stimulation (DBS) has been effective in treating various neurological and psychiatric disorders; however, its underlying mechanism hasn’t been completely understood. Fast scan cyclic voltammetry (FSCV) is a valuable tool to elucidate underlying neurotransmitter mechanisms of DBS, due to its sub-second temporal resolution and direct identification of analytes. However, since DBS-like high frequency stimulation evokes neurotransmitter release as well as extracellular pH shift, it is hard to isolate the neurotransmitter signal from the complex environment. Here we demonstrate the efficacy of a modified FSCV technique, Paired Pulse Voltammetry (PPV), in detecting dopamine (DA) release in the caudate nucleus during long-term electrical stimulation of the medial forebrain bundle (MFB) in the rat.

Methods Unlike traditional FSCV applying a single triangular waveform, PPV employs a binary waveform with a specific time gap (2.2 ms) in between the comprising pulses. DA measurement was performed with a carbon fiber microelectrode placed in the caudate nucleus and a twisted bipolar stimulating electrode in the MFB. PPV data was collected with the Wireless Instantaneous Neurochemical Concentration Sensing System (WICCS).

Results Using PPV, the detection of DA was evident throughout the long-term stimulation (5 minutes); however, without PPV, in vivo environmental changes including pH shift eventually obscured the characteristic oxidation current of DA at 0.6V. Conclusions These results indicate that PPV can be a valuable tool to accurately determine DA dynamics in a complex in vivo environment during long-term electrical stimulation.

Keywords Deep brain stimulation (DBS), Fast scan cyclic voltammetry (FSCV), Paired pulse voltammetry (PPV), Dopamine (DA), Medial forebrain bundle (MFB)

INTRODUCTION
Deep Brain Stimulation (DBS) neurosurgery has now been widely performed throughout the world, achieving therapeutic success in various neurological and psychiatric conditions [1]. Among the most prominent disorders for which this treatment has proven effective are Parkinson’s disease, essential tremor, dystonia, and recently obsessive compulsive disorder [2-8]. Despite the efficacy of DBS for a wide variety of conditions, the precise mechanism of its therapeutic action is still incompletely understood. However, techniques such as fast scan cyclic voltammetry (FSCV) have been emerging as valuable tools for mechanistic studies of DBS [9]. FSCV is an established electrochemical technique, which typically involves the application of a linearly varying electrical potential to a carbon fiber micro-electrode (CFM) and measurement of the changes in current induced by the oxidation and reduction of neurochemicals. Using FSCV, neurochemicals can be differentiated from one another and the surrounding environment on the basis of the unique voltages at which

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Springer
Effects of deep brain stimulation on speech in patients with Parkinson’s disease and dystonia


Abstract

Disorders affecting the basal ganglia can have a severe effect on speech motor control. The effect can vary depending on the pathophysiology of the basal ganglia disease but in general terms it can be classified as hypokinetic or hyperkinetic dysarthria. Despite the role of basal ganglia on speech, there is a marked discrepancy between the effect of medical and surgical treatments on limb and speech motor control. This is compounded by the complex nature of speech and communication in general, and the lack of animal models of speech motor control. The emergence of deep brain stimulation of basal ganglia structures gives us the opportunity to record systematically the effects on speech and attempt some assumptions on the role of basal ganglia on speech motor control. The aim of the present work was to examine the impact of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) for Parkinson’s disease (PD) and globus pallidus internus (GP-DBS) for dystonia on speech motor control. A consecutive series of PD and dystonia patients who underwent DBS was evaluated. Patients were studied in a prospective longitudinal manner with both clinical assessment of their speech intelligibility and acoustical analysis of their speech. The role of pre-operative clinical factors and electrical parameters of stimulation, mainly electrode positioning and voltage amplitude was systematically examined. In addition, for selected patients, tongue movements were studied using electromyography. Aerodynamic aspects of speech were also studied. The impact of speech therapy was assessed in a subgroup of patients. The clinical evaluation of speech intelligibility one and three years post STN-DBS in PD patients showed a deterioration of speech, partly related to medially placed electrodes and high amplitude of stimulation. Pre-operative predictive factors included low speech intelligibility before surgery and longer disease duration. Articulation rather than voice was most frequently affected with a distinct dysarthria type emerging, mainly hyperkinetic-dystonic, rather than hypokinetic. Traditionally, effective therapy for PD dysarthria had little to no benefit following STN-DBS. Speech following GP-DBS for dystonia did not significantly change after one year of stimulation. A subgroup of patients showed hypokinetic features, mainly reduced voice volume and fast rate of speech more typical of Parkinsonian speech. Speech changes in both STN-DBS and GP-DBS were apparent after six months of stimulation. This progressive deterioration of speech and the critical role of the electrical parameters of stimulation suggest a long-term effect of electrical stimulation of basal ganglia on speech motor control.
The Film Awakenings
A story of Dopamine Deficiency followed by Excess

Accuracy of The 1990 Film Awakenings

Andrew Clapper
University of North Carolina at Chapel Hill

Normally, films that are based upon actual events take a great deal of liberty in
changing the details of the events that they depict. Awakenings appears to be an exception to this trend. Although the names of people involved are changed, and the methodology of treatment for a disease is different, the movie seems to depict a particular disease and the drug used to treat it very accurately. The film is based upon the book with the same name, which was written by Dr. Oliver Sacks. Dr. Sacks recommended that his name be changed, and so we follow a fictional Dr. Sayer through the summer of 1969 in the Bronx, New York. Dr. Sayer uses a new drug to try to treat some patients that appear to be catatonic, and for a time he is successful. However, patients who are treated with the drug develop a tolerance for it, and soon his patients return to their former state. The movie appears to give the audience a close approximation of the symptoms of the disease, as well as the side effects of the drug that was used to treat it.

The film Awakenings begins with a depiction of one of the main characters as a child. The child is named Leonard Lowe, and he becomes one of many victims of an epidemic of encephalitis lethargica that spread worldwide from 1917 to 1928. As his sickness progresses, he is no longer able to spend time with his friends, for fear of spreading the disease and perhaps to prevent him from being helpless should he have an attack. The film then skips forward to 1969, where we see a Dr. Sayer apply for a job at a hospital in the Bronx. Although Dr. Sayer's experience is all in research with non-human subjects, the hospital is understaffed and hires him. Dr. Sayer is determined to investigate ways to improve the quality of life for his patients, despite the skepticism of his peers. Also, instead of conducting business in a routine manner as the other doctors at the hospital seem to do, Sayer dedicates himself to investigation and testing. His investigation of multiple patients with catatonic conditions leads to the discovery that many of the patients with catatonic behavior suffered from encephalitis lethargica at some point in the past. To learn more about them, Sayer consults another doctor that treated many victims of the encephalitis lethargica. Many of the patients that survived the outbreak seemed to recover for a time, but after a number of years they gradually became catatonic. A short time later, the fact that the catatonic behavior of the encephalitis patients is similar to that of Parkinson's patients, so he investigates the latest advances in Parkinson's treatments. At a conference on Parkinson's treatments, Sayer first learns about Levodopa (L Dopa). Sayer proposes that L Dopa be tried as a treatment for one of his catatonic patients, although his superiors doubt he will be successful. He selects Leonard Lowe for the first series of L
Dopa treatments. After a time, Leonard awakens from his catatonic state and his mother sees him fully conscious for the first time since he was a child. Sayer then lobbies the patrons of the hospital for additional funding to expand the L Dopa treatments to the rest of the encephalitic patients, and when they see film footage of Leonard before and after his treatments, they enthusiastically begin writing checks. Virtually all of the patients experience what appears to be a full recovery, and for a time they are able to lead the normal life that is often taken for granted. Unfortunately, it is not long before Leonard begins to experience side effects of L Dopa administration. He begins to experience convulsions, paranoia, and psychotic behavior. His body also begins to build a tolerance for it, so that his Parkinsonian symptoms begin to return. Although Dr. Sayer vows not to give up, Leonard eventually returns to his previous catatonic state. After a time, the rest of Sayer's patients experience the same course of events. The film ends with a speech given by Sayer, who reflects on the lessons that his patients taught him over the course of the previous summer.

In order to understand whether the film Awakenings is accurate, it is important to convey basic information about encephalitis lethargica. From 1917 to 1928, encephalitis lethargica was epidemic worldwide. It is estimated that over five million people died from causes related to the disease. The leading theory on the cause of encephalitis lethargica is that the disease results from a strong immune system reaction to an infection by bacterium related to streptococcus. Researchers have found that antibodies have bound themselves to neurons in the basal ganglia and midbrain in encephalitis lethargica (EL) patients. The symptoms of EL often begin with a high fever, headache, and sore throat. Other symptoms follow, including tremors, muscle pains, a slowing of physical and mental response, and drowsiness. At times, a person infected with EL may see behavioral and personality changes, and sometimes they can become psychotic. Unfortunately, there is little to be done in the way of treatment for those suffering form encephalitis besides attempting to stabilize the patient. The patient is kept hydrated with intravenous fluids and watched carefully for signs of brain swelling. If needed, they are treated with anticonvulsants to control seizures. If the disease becomes progressive, brain damage similar to that caused by Parkinson's disease can occur. Because of Dr. Oliver Sacks' work, L Dopa is considered a possible treatment for those with progressive EL, but unfortunately the periods of improved quality of life are always short lived.
An understanding of the drug L Dopa is also important to ascertaining the accuracy of Awakenings. In the 1950s, Arvid Carlsson showed that L Dopa reduced Parkinsonian symptoms in animals. Parkinson's patients tend to show degeneration of the substantia nigra. Normally, dopamine is released from most neurons in the substantia nigra, but Parkinson's patients have little dopamine present there. L Dopa, which can be metabolized into dopamine, is able to be administered as a drug because it is able to cross the blood brain barrier. Dopamine, however, can not do so. It follows that L Dopa helps return the dopamine levels in the substantia nigra to normal levels, and thus help the brain achieve a more normal state of functioning (Pinel, 2007). Unfortunately, the human body develops a tolerance of L Dopa, making its effectiveness temporary. Also, L Dopa has been associated with a number of side effects. Some side effects that correspond with events in Awakenings include confusion, extreme emotional states, excessive libido, fragmented sleep, working memory improvement, and a condition similar to amphetamine psychosis.

Awakenings appears to be extremely accurate as far as EL and L Dopa are concerned. The actors that portray EL patients with progressive states of the disease do an excellent job of simulating what is similar to catatonic behavior. In particular, Robert DeNiro as Leonard Lowe seems to portray the progression from awakening to L Dopa side effects to return to the progressive EL state well. When he is first given L Dopa in the film, he shows a gradual increase in physical and cognitive ability to what appears to be a normal state. Later, his behavior is consistent with the side affects associated with L Dopa. He shows an extreme emotional state and fragmented sleep when he calls Dr. Sayer in the middle of the night and tells him that they need to tell people not to take life for granted. Also, the film shows what may be excessive libido when Leonard shows great interest in the women he sees when he visits the city with Sayer. Leonard also has what appears to be a psychotic break, and he becomes paranoid and asks other patients at the hospital to protect him. Psychotic breaks similar to those caused by amphetamines are another known side effect of L Dopa.

Besides the fact that cars, a bus, and a jet appear in the film that were not yet being used in 1969, there exist a few more inaccuracies. Rather than starting L Dopa treatment with one patient and then expanding to all of the EL patients as depicted in the film, Oliver Sacks actually began his study as a double blind procedure with a placebo group and a treatment group. He also originally intended to conduct the study for 90 days. Once he
saw that fifty percent of his patients were showing improvement, Sacks went ahead and began giving all of the patients L Dopa and dropped the 90 day limit on the study. Sacks' decision to do so is a good example a particular bioethics issue. At times, experimental drugs do not appear to be effective or cost efficient enough to continue to be used under normal circumstances, but doctors will continue to prescribe them in order to maximize the quality of life for their patients. Instead of going from half of the patients in a double blind study to all of them, the film depicts Dr. Sayer going from one patient to all of his patients. This difference in methodology appears to be the only major difference between the events and depictions in the film and the events that the book and film are based upon (Sacks, 1983).

Awakenings is close resemblance of the actual events that took place in a Bronx hospital during the summer of 1969. A doctor there did treat a group of EL patients with L Dopa, with astonishing but short lived success. The actors in the movie simulated EL and L Dopa side effects well. Robin Williams did a good job imitating the personality and mannerisms of Oliver Sacks as the renamed Dr. Sayer. Even though Dr. Sayer uses methodology different than what was originally used by Sacks, overall the film does serve as an effective educational tool for EL and L Dopa. The praise and award nominations it received are well deserved.

References
Dopamine HCl (200 mg) in 5% Dextrose Injection USP (Dopamine HCl 800 mcg/mL)

250 mL

B. BRAUN Melsungen AG

Performance

Dopamine Levels

Depletion

Task A

Task B

Over-dosing

Electrolytes (mEq/Liter): HCO3 22-24

Sterile, nonpyrogenic: Single dose container.

Recommended Storage: Room temperature (25°C), Avoid excessive heat, Protect from freezing. See Package Insert.

Rx only

Each 100 mL contains:

Dopamine HCl 0.8 g

Sodium Metabisulfite NF (Antioxidant) 29.9 mg

Water for Injection USP q.s.

pH: 3.3 (2.8-4.8)

(May be complicated with hydroxyzine, Aminophylline or Sodium Hydration NF as required.)

Dilu. Constancy: 279 mOsml/kg/Liter

Do Not Administer Simultaneously With Blood.

For Intravenous use only. Use only if solution is clear and vacuum is present.

Each 50 mL contains: 400 mcg/kg

Each mL contains: 8 mcg/kg

For Intravenous use only. Use only if solution is clear and vacuum is present.

Each 50 mL contains: 1000 mcg/kg

Each mL contains: 20 mcg/kg

For Intravenous use only. Use only if solution is clear and vacuum is present.
Dopamine history

Dopamine was first synthesized in 1910 by George Barger and James Ewens at Wellcome Laboratories in London, England.

In 1958, Arvid Carlsson and Nils-Åke Hillarp, at the Laboratory for Chemical Pharmacology of the National Heart Institute of Sweden, discovered the function of dopamine as a neurotransmitter. Arvid Carlsson was awarded the 2000 Nobel Prize in Physiology or Medicine for showing that dopamine is not just a precursor of norepinephrine and epinephrine but a neurotransmitter, as well.
Dopamine production

Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area. It is a neurohormone that is released by the hypothalamus. Its action is as a hormone that is an inhibitor or prolactin release from the anterior lobe of the pituitary.

Dopamine Deficiency Related Symptoms and Conditions

With a dopamine deficiency, the early warning signs of deteriorating health are related to loss of energy: physically you experience fatigue, and mentally you’re sluggish. These effects can show up in your body in a variety of ways and can affect any of the four major domains of brain function.

A dopamine deficiency can cause any of these symptoms:

Physical Issues:

Anemia Excessive sleep Narcolepsy

Balance problems Food cravings Nicotine cravings

Blood sugar instability Head and facial tremor Obesity

Bone density loss High Blood Pressure Parkinson’s disease

Carbohydrate binges Hyperglycemia Slow or poor metabolism

Constipation Inability to gain or lose weight Slow or rigid movements

Decreased desire for food Joint pain Substance abuse

Decreased physical strength and activity Kidney problems Sugar or junk food cravings

Diabetes Light-headedness Tremors

Diarrhea Low sex drive Thyroid disorders

Difficulty achieving orgasm Movement disorders Trouble swallowing

Digestion problems

Personality Issues
Aggression Hedonistic behavior

Anger Inability to handle stress

Carelessness Isolating oneself from others

Depression Mood swings

Fear of being observed Procrastination

Guilt or feelings of worthlessness/ Self-destructive thoughts of hopelessness

Memory Issues:

Distractibility Lack of working memory

Failure to listen and follow instructions Poor abstract thinking

Forgetfulness Slow processing speed

Attention Issues:

Attention deficit disorder Hyperactivity

Decreased alertness Impulsive behavior

Failure to finish tasks Poor concentration

Obviously, no one person will have all of the listed symptoms of dopamine deficiency at once. Yet all of these symptoms are treated every day by thousands of doctors, most of whom overlook or may be unaware of the fact that they are caused by a dopamine deficiency.

Dopamine Deficiency

Deficiency of dopamine is known to be responsible for Parkinson’s disease. Patients suffering from this condition have problems with the movement and speech. This chronic and progressive disease causes tremor, muscle strictness, slow movements and sometimes even complete loss of movement. Speech problems occur in later stages of the disease and are associated with the impaired memory and learning skills.

Patients diagnosed with the lack of DA often experience sleeping problems. In some cases, lack of dopamine may cause excess sleep.

Dopamine deficiency might be characterized by the development of addiction to various stimulants, coffee being one of the relatively harmless ones.

People diagnosed with lack of dopamine are often overweight, with low blood pressure (hypotension) and dehydration. Hypotension may occur in the morning, when the patient
tries to get up from the bed and leads to dizziness. Another symptom connected to the dopamine deficiency is low blood sugar level.

Many of the patients with lack of dopamine experience sexual problems (impotence, low libido), depression, suicidal ideas, motivation problems and incapacity to feel the pleasure in anything.
Neurotransmitters with discrete localization within the brain. A) The chemical structure of the monoamine neurotransmitter dopamine and a schematic drawing of the localization of dopamine-containing neurons in the human and rat brain and the sites where dopamine-
containing axons are found. B) The chemical structure of the monoamine neurotransmitter serotonin and similar brain map showing locations of serotonin-containing cells and their axons.

**Dopamine receptors**

Dopamine acts on receptors that are specific for it. Five subtypes of mammalian dopamine receptors are grouped into two classes.

- D1-like receptor class – This comprises of D1 and D5 receptor subtypes
- D2-like receptor class – This comprises of D2, D3, and D4 receptor subtypes

These receptors have similar signalling properties. They however have different signal transduction pathways that determine their subtypes and classes.

All of the dopamine receptors are G protein-coupled receptors (GPCRs), who’s signalling is primarily mediated by interaction with and activation of GTP-binding proteins (G proteins). Members of this superfamily are also called 7-transmembrane receptors because they traverse the cell membrane seven times. They are also called serpentine receptors because of the snake like manner in which they wind back and forth across the membrane.

**Actions of dopamine**

Dopamine is also used as medication. It acts on the sympathetic nervous system. Application of dopamine leads to increased heart rate and blood pressure.

Dopamine cannot cross the blood-brain barrier, so dopamine given as a drug does not directly affect the central nervous system.

Dopamine is needed in some brain diseases as well. This includes diseases such as Parkinson's disease and dopa-responsive dystonia. For these patients levodopa is used. This is a precursor of dopamine. It can cross the blood-brain barrier.
How to Increase Dopamine

The dopamine naturally produced by your brain makes you feel good. You get a rush of dopamine in response to pleasurable activities like food or sex. On the other hand, without enough dopamine, you may feel sluggish, depressed and uninterested in life. Try some different methods to boost your dopamine levels if you're feeling a little low.

Steps

**Method 1: Increase Dopamine Through Diet, Exercise and Adequate Sleep**

**Eat foods rich in tyrosine.** Almonds, avocados, bananas, low-fat dairy, lima beans, sesame seeds and pumpkin seeds may all help your body to produce more dopamine.

**Increase your intake of antioxidants.** Dopamine is easy to oxidize, and antioxidants may reduce free radical damage to the brain cells that produce dopamine. Many fruits and vegetables are rich in antioxidants, including:

- **Beta-carotene and carotenoids:** Greens, orange vegetables and fruits, asparagus, broccoli, beets
- **Vitamin C:** Peppers, oranges, strawberries, cauliflower, Brussels sprouts

[1]
*Vitamin E*: Nuts and sunflower seeds, greens, broccoli, carrots[^2]

**Avoid food that inhibits brain function.** Such foods may include refined packaged foods, refined white flour, cholesterol, caffeine, and saturated fats.[^3]

**Exercise regularly.** Exercise increases blood calcium, which stimulates dopamine production and uptake in your brain. Try 30 to 60 minutes of walking, swimming or jogging to jump-start your dopamine

**Get plenty of sleep.** Your brain uses very little dopamine while you sleep, which helps you to build up your supply naturally for the next day. Get at least 8 hours of sleep per night.

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**Method 2: Increase Dopamine By Taking Supplements or Medication**
Try a supplement. Some physicians recommend Vitamin B6 supplements and L-Phenylalanine to elevate dopamine in the brain. You can grab either of these at your local drugstore.⁴

To Make the Serotonin Dopamine Tonic take enough Banana peels to fill a moderate sized bowel. Crush softly and cover with good quality Vodka 20% Alcohol and 10% fruit sugar. Let stand for 2 to 3 days in a cool dry place cover with towel. Crush once more the wet mixture and, strain with coarse strainer. The pasty mixture can be served with milk. take 4 oz wait 30 min and see if it helps. Use another 4 oz if you need to sedate tremors or relieve depression.
To make the Serotonin and Dopamine Gum
Take a Banana peel it and insert a stick of gum into the place and fold over the peel. Let it set for 2 to 3 days in a cool place. The gum will absorb the serotonin and dopamine. Place the gum back into the wrapper and chew it when you need a little euphoria. Use it to treat depression or Parkinson's tremors.
A gene that regulates dopamine levels in the brain is involved in the development of schizophrenia in children at high risk for the disorder, say researchers at the Stanford University School of Medicine, Lucile Packard Children’s Hospital and the University of Geneva.

The finding adds to mounting evidence of dopamine's link to psychiatric and neurological disorders. It may also allow physicians to pinpoint a subset of these children for treatment before symptoms start.

"The hope is that we will one day be able to identify the highest-risk groups and intervene early to prevent a lifetime of problems and suffering," said Allan L. Reiss, MD. "As we gain a much better understanding of these disorders, we can design treatments that are much more specific and effective."

Reiss is the Robbins Professor of Psychiatry and Behavioral Sciences at Stanford and director of the school's Center for Interdisciplinary Brain Sciences Research. He is also a child and adolescent psychiatrist at Packard Children's Hospital at Stanford. The research,
Dopamine levels have been implicated in many neurological conditions, including Parkinson’s disease and psychosis. Data from this and other studies suggest a kind of Goldilocks effect for this important chemical messenger: too little or too much can dramatically interfere with normal cognition, behavior and motor skills. Nudging these levels back into the "just-right" range may help treat or cure some conditions.

Schizophrenia is a brain disease that affects about 1 percent of people in this country and can manifest itself through agitation, catatonia and psychosis. Although the disorder sometimes runs in families, it can also occur spontaneously. Scientists have suspected for many years that dopamine was involved, due in part to the success of older psychiatric drugs that function by interacting with dopamine receptors in the brain. But the root cause of schizophrenia has remained elusive.

Reiss and the study's first author Doron Gothelf, MD, a child psychiatrist and postdoctoral scholar at Stanford, studied 24 children with a small deletion in one copy of chromosome 22. About 30 percent of children with this deletion, which occurs in about one in 4,000 births, will develop schizophrenia or a related psychotic disorder. These children also often have special facial features, cardiac defects and cleft anomalies that often make their speech hypernasal. Although these characteristics make it possible to identify them before psychiatric disorders develop, the disorder, called velocardiofacial syndrome, is under-diagnosed and under-recognized in this country despite its link to schizophrenia.

"We have strong evidence that this deletion is a major risk factor for the development of schizophrenia or related psychotic disorders," said Reiss. "We asked, 'What is it about this deletion that causes such an increase in risk?"

The answer lay in the fact that one of the missing genes encodes a dopamine-degrading protein called COMT. Natural variations in the gene generate two versions of the protein: one with high activity, one with low.

Because most people have two copies of the gene, it doesn't usually matter which versions of COMT they inherit; high-high, high-low and low-low all seem to provide enough COMT activity to get the job done (though some combinations confer a mild advantage for some cognitive tasks).

But children with the deletion have only the one copy that remains on their intact chromosome 22. Reiss and Gothelf, who is also an assistant professor at Tel Aviv University in Israel, surmised that a single copy of the low-activity COMT might not dispose of enough dopamine to produce optimal brain function. They set out to determine if the clinical course of the children with deletions who developed schizophrenia varied with the version of the COMT protein they had.
The researchers matched the age, gender, ethnicity and IQ of the 24 children with the deletion with 23 children with developmental disabilities of unknown causes. They then tested their subjects' verbal IQ and cognitive abilities. None of the children in either group had yet experienced any psychotic symptoms. They also measured the size of the children's prefrontal cortex - an area of the brain where COMT activity is particularly important and that is strongly associated with schizophrenia. They repeated the same tests after about five years, when their subjects reached late adolescence or early adulthood.

As expected, about 29 percent, or seven, of the children with the deletion had developed a psychotic disorder by the second round of testing, compared with only one child in the control group. Of these seven, those with the low-activity version of COMT had experienced a significantly greater drop in their verbal IQ and expressive language skills and a markedly greater decrease in the volume of their prefrontal cortex than did their peers with the more highly active version of COMT. The psychotic symptoms of the low-activity subset were also significantly more severe.

In contrast, members of the control group experienced no significant differences in any of these categories, regardless of their COMT profiles.

"What's interesting about this finding is that the disease course in the individuals with low-activity COMT looked remarkably like idiopathic schizophrenia," said Reiss, who hopes to use this and future data to develop a model for other causes of schizophrenia.

"Although this deletion probably causes less than 5 percent of schizophrenia cases, it's the only well-defined genetic risk factor we have right now," said Reiss. "In the future, researchers will likely discover multiple causes of this disorder, with complex interactions between genetic and environmental risk factors. But COMT activity appears to be an important contributory factor for the development of psychosis in the chromosome 22 deletion syndrome."

The researchers next plan to extend their studies to younger children, and to repeat the above study using multiple time points to more precisely catch the ongoing development of the disorder.

http://www.med.stanford.edu/
Dopamine

Dopamine (abbreviated as DA[1]), is a monoamine neurotransmitter and hormone, which has a number of important physiological roles in the bodies of animals. Dopamine is a simple organic chemical in the catecholamine family and may also be classified as a substituted phenethylamine. Its name derives from its chemical structure, which consists of an amine group (NH$_2$) linked to a catechol structure, called dihydroxyphenethylamine, the decarboxylated form of dihydroxyphenylalanine (acronym DOPA).

In the brain, dopamine functions as a neurotransmitter—a chemical released by nerve cells to send signals to other nerve cells. The human brain uses five known types of dopamine receptors, labeled $D_1$, $D_2$, $D_3$, $D_4$, and $D_5$. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area.

Dopamine plays a major role in the brain system that is responsible for reward-driven learning. Every type of reward that has been studied increases the level of dopamine transmission in the brain, and a variety of addictive drugs, including stimulants such as cocaine, amphetamine, and methamphetamine, act directly on the dopamine system.[2] Personality traits such as extraversion and reward seeking have been linked to higher sensitivity to rewarding stimuli of the mesolimbic dopamine system.[3]

Several important diseases of the nervous system are associated with dysfunctions of the dopamine system. Parkinson's disease, an age-related degenerative condition causing tremor and motor impairment, is
caused by loss of dopamine-secreting neurons in the substantia nigra. Schizophrenia has been shown to involve elevated levels of dopamine activity in the mesolimbic pathway and decreased levels of dopamine in the prefrontal cortex. Attention deficit hyperactivity disorder (ADHD) and restless legs syndrome (RLS) are also believed to be associated with decreased dopamine activity.

Dopamine is available as an intravenous medication acting on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. However, because dopamine cannot cross the blood–brain barrier, dopamine given as a drug does not directly affect the central nervous system. To increase the amount of dopamine in the brains of patients with diseases such as Parkinson’s disease and dopa-responsive dystonia, L-DOPA (the precursor of dopamine) is often given because it crosses the blood–brain barrier relatively easily.

History

Main article: History of catecholamine research

Dopamine was first synthesized in 1910 by George Barger and James Ewens at Wellcome Laboratories in London, England. It was named dopamine because it is a monoamine whose precursor in the Barger-Ewens synthesis is 3,4-dihydroxyphenylalanine (levodopamine or L-DOPA). Dopamine’s function as a neurotransmitter was first recognized in 1958 by Arvid Carlsson and Nils-Åke Hillarp at the Laboratory for Chemical Pharmacology of the National Heart Institute of Sweden. Carlsson was awarded the 2000 Nobel Prize in Physiology or Medicine for showing that dopamine is not only a precursor of norepinephrine (noradrenaline) and epinephrine (adrenaline), but also a neurotransmitter.
Catecholamine biosynthesis

Dopamine is synthesized in the body from within cells (mainly by neurons and cells in the medulla of the adrenal glands) and can be created from any one of the following three amino acids:

- **L-Phenylalanine** (PHE)
- **L-Tyrosine** (L-4-hydroxyphenylalanine; TYR)
L-DOPA (L-3,4-dihydroxyphenylalanine; DOPA)

These amino acids are provided from natural sources such as the ingestion of various kinds of food, with L-tyrosine being the most common of the three. Although dopamine itself is also commonly found in many types of food, unlike the amino acids that form it, it is incapable of crossing the protective blood–brain barrier (BBB), which severely restricts its functionality upon consumption. It must be formed from within the walls of the BBB to properly perform its cognitive duties, though not its peripheral actions. Dopamine itself is also used in the synthesis of the following related catecholamine neurotransmitters:

- Norepinephrine (β,3,4-trihydroxyphenethylamine; Noradrenaline; NE, NA)
- Epinephrine (β,3-dihydroxy-N-methylphenethylamine; Adrenaline; EPI, ADR)

This is the complete metabolic pathway:

L-Phenylalanine → L-Tyrosine → L-DOPA → Dopamine → Norepinephrine → Epinephrine

L-Phenylalanine is converted into L-tyrosine by the enzyme phenylalanine hydroxylase (PAH) with molecular oxygen (O₂) and tetrahydrobiopterin (THB) as cofactors. L-Tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase (TH) with tetrahydrobiopterin (THB), O₂, and ferrous iron (Fe²⁺) as cofactors. L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (AAAD; also known as DOPA decarboxylase (DDC)) with pyridoxal phosphate (PLP) as the cofactor. The reactions are illustrated as follows:

- PAH: L-Phenylalanine + THB + O₂ + Fe²⁺ → L-Tyrosine + DHB + H₂O + Fe²⁺
- TH: L-Tyrosine + THB + O₂ + Fe²⁺ → L-DOPA + DHFA + H₂O + Fe²⁺
- AAAD: L-DOPA + PLP → Dopamine + PLP + CO₂

Dopamine is converted into norepinephrine by the enzyme dopamine β-hydroxylase (DBH) with O₂ and L-ascorbic acid as cofactors. Finally, norepinephrine is converted into epinephrine by the enzyme phenylethanolamine N-methyltransferase (PNMT) with S-adenosyl-L-methionine (SAMe) as the cofactor. The reactions are illustrated as follows:

- DBH: Dopamine + Ascorbic Acid + O₂ → Norepinephrine + DHA + H₂O
- PNMT: Norepinephrine + SAMe → Epinephrine + Homocysteine

It should be noted that some of the cofactors also require their own synthesis. These include:

- Guanine → Guanosine → Guanosine Monophosphate (GMP) → Guanosine Diphosphate (GDP) → Guanosine Triphosphate (GTP)
- GTP Cyclohydrolase I (GTPCH, GCH): GTP → 7,8-Dihydروneopterin Triphosphate (DHNTP)
- 6-Pyruvoyltetrahydropterin Synthase (PTS, PTPS): DHNTP → 6-Pyruvoyltetrahydropterin (Dyspropterin)
- Sepiapterin Reductase (SPR): Dyspropterin → Tetrahydrobiopterin (THB)

- Folic Acid → DHFA → THFA
- Pyridoxine → Pyridoxamine → Pyridoxal → PLP (requires Zn²⁺ as a cofactor)
Deficiency in any required amino acid or cofactor will result in subsequent dopamine, norepinephrine, and epinephrine biosynthesis impairment and deficiency as well. Conversely, supplementation with L-phenylalanine, L-tyrosine, L-DOPA, or any of the cofactors will increase their respective concentrations.

Storage, release, and reuptake

Upon synthesis, dopamine is transported from the cell cytosol into synaptic vesicles by the vesicular monoamine transporter 2 (VMAT2). Dopamine is stored in and remains in these vesicles until an action potential occurs and forces them to merge with the cell membrane via a process known as exocytosis, thereby dumping dopamine into synapses.

Once in the synapse, dopamine binds to and activates postsynaptic dopamine receptors, resulting in the signal of the presynaptic cell being propagated to the postsynaptic neuron. Dopamine also binds to presynaptic dopamine receptors, which can either excite the presynaptic cell or inhibit it depending on their electrical potential. Presynaptic receptors with an inhibitory potential are called autoreceptors and inhibit neurotransmitter synthesis and release. They serve to keep dopamine levels normalized in certain pathways when release is acutely disrupted and becomes too high or too low.

After dopamine has performed its synaptic duties, it is taken up via reuptake back into the presynaptic cell by either the high-affinity dopamine transporter (DAT) or the low-affinity plasma membrane monoamine transporter (PMAT). Once back in the cytosol, it is subsequently repackaged into vesicles by VMAT2.

Degradation
Dopamine degradation

Dopamine is directly broken down into inactive metabolites by two enzymes, monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). It is equally metabolized by the two respective isoforms of MAO, MAO-A and MAO-B.

Dopamine is metabolized by MAO into 3,4-dihydroxyphenyacetaldehyde (DOPAL). DOPAL is further metabolized into 3,4-dihydroxyphenylacetic acid (DOPAC) by the enzyme aldehyde dehydrogenase (ALDH). DOPAL can also be reduced to 3,4-dihydroxyphenylethanol (DOPET; also known as hydroxytyrosol) by aldose reductase (AR) to a lesser extent. Finally, COMT reduces DOPAC and DOPET to homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylethanol (MOPET), respectively, which are then excreted in the urine. COMT can also directly metabolize dopamine into 3-methoxytyramine (3-MT), which is then subsequently metabolized to HVA by MAO and is excreted in the urine as well. The reactions are illustrated and summarized here:

- Dopamine → DOPAL → DOPAC → HVA
- Dopamine → DOPAL → DOPET → MOPET
- Dopamine → 3-MT → HVA
In most areas of the brain, including the striatum and basal ganglia, dopamine is inactivated by reuptake via the DAT, then enzymatic breakdown by MAO into DOPAC. In the prefrontal cortex, however, there are very few DAT proteins, and dopamine is inactivated instead by reuptake via the norepinephrine transporter (NET), presumably on neighboring norepinephrine neurons, then enzymatic breakdown by COMT into 3-MT. The DAT pathway is roughly an order of magnitude faster than the NET pathway: in mice, dopamine concentrations decay with a half-life of 200 milliseconds in the caudate nucleus (which uses the DAT pathway) versus 2,000 milliseconds in the prefrontal cortex. Dopamine that is not broken down by enzymes is repackaged into vesicles for reuse by VMAT2.
Dopamine binds to and activates a group of receptors called the dopamine receptors to mediate its physiological effects in the body. The dopamine receptors are a series of five G protein-coupled receptors (GPCRs), which consist of the D₁, D₂, D₃, D₄, and D₅ receptors. As GPCRs, they work by modulating the cyclic adenosine monophosphate (cAMP) second messenger system to produce a cellular response. The five receptors are individually categorized into two distinctive groups based on their varying properties and effects, the D₁-like and D₂-like subfamilies. The D₁ and D₅ receptors belong to the D₁-like subfamily. They are coupled to Gs and increase the cellular concentrations of cAMP by the activation of the enzyme adenylate cyclase. The D₂, D₃, and D₄ receptors belong to the D₂-like subfamily. They are coupled to Gi/Go and decrease the cellular concentrations of cAMP by inhibition of adenylate cyclase. Ultimately, the cAMP second messenger system, through several downstream mechanisms, works by modulating the opening of plasmalemmal ion channels that allow positively charged ions such as Na⁺ and K⁺ to enter or exit the cytoplasm of the cell, thereby generating or inhibiting an action potential. The receptors also couple directly to ion channels via the G-proteins. The D₁-like receptors have various effects on neuronal activity, while the D₂-like receptors tend to decrease action potential generation and are therefore usually inhibitory.

<table>
<thead>
<tr>
<th>Family</th>
<th>Receptor</th>
<th>Gene</th>
<th>Type</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁-like</td>
<td>D₁</td>
<td>DRD1</td>
<td>Gₛ-coupled.</td>
<td>Increasing intracellular levels of cAMP by activating adenylate cyclase.</td>
</tr>
<tr>
<td></td>
<td>D₂</td>
<td>DRD5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₂-like</td>
<td>D₂</td>
<td>DRD2</td>
<td>Gₛ/Gₒ-coupled.</td>
<td>Decreasing intracellular levels of cAMP by inhibiting adenylate cyclase.</td>
</tr>
<tr>
<td></td>
<td>D₃</td>
<td>DRD3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D₄</td>
<td>DRD4</td>
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</table>

The D₁ receptor is the most widespread dopamine receptor in the central nervous system. The D₃, D₄, and D₅ receptors are present in significantly lower levels than are the D₁ and D₂ receptors. In fact, the D₁ receptors are approximately 100x more common than the D₅ receptors. However, dopamine binds to the D₃, D₄, and D₅ receptors with nanomolar or submicromolar affinity constants, while its corresponding
constants for D₁ and D₂ receptors are in the micromolar ranges. As an example, dopamine has 20-fold higher binding affinity for the D₃ receptor in comparison to the D₂ receptor, and 10-fold higher binding affinity for the D₅ receptor over the D₁ receptor. Hence, overall activation of the system seem to be more or less well-balanced.

Functions in the brain
Dopamine pathways. In the brain, dopamine plays an important role in the regulation of reward and movement. As part of the reward pathway, dopamine is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus accumbens and the prefrontal cortex. Its motor functions are linked to a separate pathway, with cell bodies in the substantia nigra that manufacture and release dopamine into the striatum.

Dopamine has many functions in the brain, including important roles in behavior and cognition, voluntary movement, motivation, punishment and reward, inhibition of prolactin production (involved in lactation and sexual gratification), sleep, dreaming, mood, attention, working memory, and learning. Dopaminergic neurons (i.e., neurons whose primary neurotransmitter is dopamine) are present chiefly in the ventral tegmental area (VTA) of the midbrain, the substantia nigra pars compacta, and the arcuate nucleus of the hypothalamus.

It has been hypothesized that dopamine transmits reward prediction error, although this has been questioned. According to this hypothesis, the phasic responses of dopamine neurons are observed when an unexpected reward is presented. These responses transfer to the onset of a conditioned stimulus after repeated pairings with the reward. Further, dopamine neurons are depressed when the expected reward is omitted. Thus, dopamine neurons seem to encode the prediction error of rewarding outcomes. In nature, we learn to repeat behaviors that lead to maximizing rewards. Dopamine is therefore believed to provide a teaching signal to parts of the brain responsible for acquiring new behavior. Temporal difference learningprovides a computational model describing how the prediction error of dopamine neurons is used as a teaching signal. The reward system in insects uses octopamine, which is the presumed arthropod homolog of norepinephrine rather than dopamine. In insects, dopamine acts instead as a punishment signal and is necessary to form aversive memories.

**Anatomy**

*Main article: Dopaminergic pathways*

Dopaminergic neurons form a neurotransmitter system which originates in substantia nigra pars compacta, ventral tegmental area (VTA), and hypothalamus. These project axons to large areas of the brain which are typically divided into four major pathways:

- **Mesocortical pathway** connects the ventral tegmental area to the frontal lobe of the pre-frontal cortex. Neurons with somas in the ventral tegmental area project axons into the pre-frontal cortex.
- **Mesolimbic pathway** carries dopamine from the ventral tegmental area to the nucleus accumbens via the amygdala and hippocampus. The somas of the projecting neurons are in the ventral tegmental area.
- **Nigrostriatal pathway** runs from the substantia nigra to the neostriatum. Somas in the substantia nigra project axons into the caudate nucleus and putamen. The pathway is involved in the basal ganglia motor loop.
- **Tuberoinfundibular pathway** runs from the hypothalamus to the pituitary gland.
This innervation explains many of the effects of activating this dopamine system. For instance, the mesolimbic pathway connects the VTA and nucleus accumbens; both are central to the brain reward system. Whilst the distinction between pathways is widely used, and is regarded as a "convenient heuristic when considering the dopamine system", it is not absolute, and there is some overlap in the projection targets of each group of neurons.

**Cellular effects**

**Tonic and phasic activity**

The level of extracellular dopamine is modulated by two mechanisms: tonic and phasic dopamine transmission. Tonic dopamine transmission occurs when small amounts of dopamine are released independently of neuronal activity, and is regulated by the activity of other neurons and neurotransmitter reuptake. Phasic dopamine release results from the activity of the dopamine-containing cells themselves. This activity is characterized by irregular pacemaking activity of single spikes, and rapid bursts of typically 2-6 spikes in quick succession. Concentrated bursts of activity result in a greater increase of extracellular dopamine levels than would be expected from the same number of spikes distributed over a longer period of time.

**Reuptake inhibition and synaptic release**

Cocaine and amphetamines inhibit the re-uptake of dopamine; however, they influence separate mechanisms of action. Cocaine is a dopamine transporter and norepinephrine transporter blocker that competitively inhibits dopamine uptake to increase the lifetime of dopamine and augments an overabundance of dopamine (an increase of up to 150 percent) within the parameters of the dopamine neurotransmitters. Like cocaine, amphetamines increase the concentration of dopamine in the synaptic gap, but by a different mechanism. Amphetamines and methamphetamine are similar in structure to dopamine, and so can enter the terminal bouton of the presynaptic neuron via its dopamine transporters as well as by diffusing through the neural membrane directly. By entering the presynaptic neuron, amphetamines force dopamine molecules out of their storage vesicles and expel them into the synaptic gap by making the dopamine transporters work in reverse.

**Motor control**

Dopamine reduces the influence of the indirect pathway while increasing the actions of the direct pathway within the basal ganglia. Insufficient dopamine biosynthesis in the dopaminergic neurons can cause Parkinson's disease, a condition in which one loses the ability to execute smooth, controlled movements.

**Regulating prolactin secretion**

Dopamine is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is secreted into the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion. Thus, in the context of regulating prolactin secretion, dopamine is occasionally called prolactin-inhibiting factor (PIF), prolactin-inhibiting hormone (PIH), or prolactostatin.
Cognition and frontal

In the frontal lobes, dopamine controls the flow of information from other areas of the brain. Dopamine disorders in this region of the brain can cause a decline in neurocognitive functions, especially memory, attention, and problem-solving. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to attention deficit disorder. It has been found that D1 receptors as well as D4 receptors are responsible for the cognitive-enhancing effects of dopamine, whereas D2 receptors are more specific for motor actions.

Chemoreceptor trigger zone

Dopamine is one of the neurotransmitters implicated in the control of nausea and vomiting via interactions in the chemoreceptor trigger zone. Metoclopramide is a D2-receptor antagonist that functions as a prokinetic/antiemetic.

Effects of drugs that reduce dopamine activity

In humans, drugs that reduce dopamine activity (neuroleptics, e.g. antipsychotics) have been shown to impair concentration, reduce motivation, cause anhedonia (inability to experience pleasure), and long-term use has been associated with tardive dyskinesia, an irreversible movement disorder. Antipsychotics have significant effects on gonadal hormones including significantly lower levels of estradiol and progesterone in women, whereas men display significantly lower levels of testosterone and DHEA when undergoing antipsychotic drug treatment compared to controls. Antipsychotics are known to cause hyperprolactinaemia leading to amenorrhea, cessation of normal cyclic ovarian function, loss of libido, occasional hirsutism, false positive pregnancy tests, and long-term risk of osteoporosis in women. The effects of hyperprolactinemia in men aregynaecomastia, lactation, impotence, loss of libido, and hypospermatogenesis. Furthermore, antipsychotic drugs are associated with weight gain, diabetes, drooling, dysphoria (abnormal depression and discontent), fatigue, sexual dysfunction, heart rhythm problems, stroke and heart attack.

Selective D2/D3 agonists pramipexole and ropinirole, used to treat restless legs syndrome (RLS), have limited anti-anhedonic properties as measured by the Snaith-Hamilton Pleasure Scale (SHAPS).

Opioid and cannabinoid transmission

Opioid and cannabinoid transmission instead of dopamine may modulate consummatory pleasure and food palatability (liking). This could explain why animals' liking of food is independent of brain dopamine concentration. Other consummatory pleasures, however, may be more associated with dopamine. One study found that both anticipatory and consummatory measures of sexual behavior (male rats) were disrupted by DA receptor antagonists. Libido can be increased by drugs that affect dopamine, but not by drugs that affect opioid peptides or other neurotransmitters.

Learning, reinforcement, and reward-seeking behavior

Dopamine is commonly associated with the reward system of the brain, providing feelings of enjoyment and reinforcement to motivate a person to perform certain activities. Dopamine is released (particularly in areas such as the nucleus accumbens and prefrontal cortex) as a result of rewarding experiences such as food, sex, drugs, and neutral stimuli that become associated with them. Recent studies indicate that aggression may also stimulate the release of dopamine in this way.
This theory can be discussed in terms of drugs such as cocaine, nicotine, and amphetamines, which directly or indirectly lead to an increase of dopamine in the mesolimbic reward pathway of the brain, and in relation to neurobiological theories of chemical addiction (not to be confused with psychological dependence), arguing that this dopamine pathway is pathologically altered in addicted persons.[43] In recent studies, cholinergic inactivation of the nucleus accumbens was able to disrupt the acquisition of drug reinforced behaviors, suggesting that dopamine has a more limited involvement in the acquisition of both drug self-administration and drug-conditioned place-preference behaviors than previously thought.[44][45]

Dopaminergic neurons of the midbrain are the main source of dopamine in the brain.[41] Dopamine has been shown to be involved in the control of movements, the signaling of error in prediction of reward, motivation, and cognition. Cerebral dopamine depletion is the hallmark of Parkinson's disease.[41] Other pathological states have also been associated with dopamine dysfunction, such as schizophrenia, autism, and attention deficit hyperactivity disorder, as well as drug abuse.

Dopamine is closely associated with reward-seeking behaviors, such as approach, consumption, and addiction.[41] Recent research suggests that the firing of dopaminergic neurons is motivational as a consequence of reward-anticipation. This hypothesis is based on the evidence that, when a reward is greater than expected, the firing of certain dopaminergic neurons increases, which consequently increases desire or motivation towards the reward.[41] However, recent research finds that while some dopaminergic neurons react in the way expected of reward neurons, others do not and seem to respond in regard to unpredictability.[46] This research finds the reward neurons predominate in the ventromedial region in the substantia nigra pars compacta as well as the ventral tegmental area. Neurons in these areas project mainly to the ventral striatum and thus might transmit value-related information in regard to reward values.[46] The nonreward neurons are predominate in the dorsolateral area of the substantia nigra pars compacta which projects to the dorsal striatum and may relate to orienting behaviour.[46] It has been suggested that the difference between these two types of dopaminergic neurons arises from their input: reward-linked ones have input from the basal forebrain, while the nonreward-related ones from the lateral habenula.[46]

### Animal studies

Clues to dopamine's role in motivation, desire, and pleasure have come from studies performed on animals. In one such study, rats were depleted of dopamine by up to 99 percent in the nucleus accumbens and neostriatum using 6-hydroxydopamine.[41] With this large reduction in dopamine, the rats would no longer eat of their own volition. The researchers then force-fed the rats food and noted whether they had the proper facial expressions indicating whether they liked or disliked it. The researchers of this study concluded that the reduction in dopamine did not reduce the rat's consummatory pleasure, only the desire to eat. In another study, mutant hyperdopaminergic (increased dopamine) mice show higher "wanting" but not "liking" of sweet rewards.[47] Mice who cannot synthesize dopamine are unable to feed sufficiently to survive more than a few weeks after birth, but will feed normally and survive if administered L-DOPA.[48]

Dopamine modulates foraging behavior in animals, by activating brain systems registering reward when food sources are found.[49] When monkeys are given a highly palatable food, dopamine levels rise, but levels then decline when the palatable food is available for prolonged periods of time and is no longer novel.[50]
Salience

Further information: Incentive salience

Dopamine may also have a role in the salience of potentially important stimuli, such as sources of reward or of danger. This hypothesis argues that dopamine assists decision-making by influencing the priority, or level of desire, of such stimuli to the person concerned.

Dopamine’s role in experiencing pleasure has been questioned by several researchers. It has been argued that dopamine is more associated with anticipatory desire and motivation (commonly referred to as "wanting") as opposed to actual consummatory pleasure (commonly referred to as "liking").

Latent inhibition and creative drive

Dopamine in the mesolimbic pathway increases general arousal and goal directed behaviors and decreases latent inhibition; all three effects increase the creative drive of idea generation. This has led to a three-factor model of creativity involving the frontal lobes, the temporal lobes, and mesolimbic dopamine.

Sociability

Since dopamine drives reward-seeking behavior and successive sensations of contentment from social interactions, sociability is also closely tied to dopamine neurotransmission. Low D2 receptor-binding is found in people with social anxiety. Traits common to negative schizophrenia (social withdrawal, apathy, anhedonia) are thought to be related to a hypodopaminergic state in certain areas of the brain. In instances of bipolar disorder, manic subjects can become hypersocial, as well as hypersexual. This is credited to an increase in dopamine, because mania can be reduced by dopamine-blocking antipsychotics.

Processing of pain

Dopamine has been demonstrated to play a role in pain processing in multiple levels of the central nervous system including the spinal cord, periaqueductal gray (PAG), thalamus, basal ganglia, insular cortex, and cingulate cortex. Accordingly, decreased levels of dopamine have been associated with painful symptoms that frequently occur in Parkinson's disease. Abnormalities in dopaminergic neurotransmission have also been demonstrated in painful clinical conditions, including burning mouth syndrome, fibromyalgia, and restless legs syndrome. In general, the analgesic capacity of dopamine occurs as a result of dopamine D2 receptor activation; however, exceptions to this exist in the PAG, in which dopamine D1 receptor activation attenuates pain presumably via activation of neurons involved in descending inhibition. In addition, D1 receptor activation in the insular cortex appears to attenuate subsequent pain-related behavior.

Behavior disorders

Deficient dopamine neurotransmission is implicated in attention-deficit hyperactivity disorder, and stimulant medications that are used to treat its symptoms increase dopamine neurotransmission. Consistent with this hypothesis, dopaminergic pathways have a role in inhibitory action control and the inhibition of the tendency to make unwanted actions.

The long-term use of levodopa in Parkinson's disease has been linked to dopamine dysregulation syndrome.
**Dopaminergic mind hypothesis**

The dopaminergic mind hypothesis seeks to explain the differences between modern humans and their hominid relatives by focusing on changes in dopamine.\(^{[72]}\) It theorizes that increased levels of dopamine were part of a general physiological adaptation due to an increased consumption of meat around two million years ago in *Homo habilis*, and later enhanced by changes in diet and other environmental and social factors beginning approximately 80,000 years ago. Under this theory, the "high-dopamine" personality is characterized by high intelligence, a sense of personal destiny, a religious/cosmic preoccupation, an obsession with achieving goals and conquests, an emotional detachment that in many cases leads to ruthlessness, and a risk-taking mentality. High levels of dopamine are proposed to underlie increased psychological disorders in industrialized societies. According to this hypothesis, a "dopaminergic society" is an extremely goal-oriented, fast-paced, and even manic society, "given that dopamine is known to increase activity levels, speed up our internal clocks and create a preference for novel over unchanging environments."\(^{[72]}\) In the same way that high-dopamine individuals lack empathy and exhibit a more masculine behavioral style, dopaminergic societies are "typified by more conquest, competition, and aggression than nurturance and communality."\(^{[72]}\) Although behavioral evidence and some indirect anatomical evidence (e.g., enlargement of the dopamine-rich striatum in humans)\(^{[72]}\) support a dopaminergic expansion in humans, there is still no direct evidence that dopamine levels are markedly higher in humans relative to other apes.\(^{[74]}\) However, recent discoveries about the sea-side settlements of early man may provide evidence of dietary changes consistent with this hypothesis.\(^{[75]}\)

**Links to psychosis**

*Main article: Dopamine hypothesis of schizophrenia*

Abnormally high dopaminergic transmission has been linked to psychosis and schizophrenia.\(^{[76]}\) However, clinical studies relating schizophrenia to brain dopamine metabolism have ranged from controversial to negative, with HVA levels in the CSF the same for schizophrenics and controls.\(^{[77]}\) Increased dopaminergic functional activity, specifically in the mesolimbic pathway, is found in schizophrenic individuals. However, decreased activity in another dopaminergic pathway, the mesocortical pathway, may also be involved. The two pathways are thought to be responsible for differing sets of symptoms seen in schizophrenia.\(^{[citation needed]}\)

**Antipsychotic medications** act largely as dopamine antagonists, inhibiting dopamine at the receptor level, and thereby blocking the effects of the neurochemical in a dose-dependant manner. The older, so-called typical antipsychotics most commonly act on D2 receptors,\(^{[78]}\) while the atypical drugs also act on D1, D3 and D4 receptors, though they have a lower affinity for dopamine receptors in general.\(^{[79][80]}\) The finding that drugs such as amphetamines, methamphetamine and cocaine, which can increase dopamine levels by more than tenfold,\(^{[81]}\) can temporarily cause psychosis, provides further evidence for this link.\(^{[82]}\) However, many non-dopaminergic drugs can induce acute and chronic psychosis.\(^{[83]}\) The NMDA antagonists Ketamine and PCP both are used in research to reproduce the positive and negative symptoms commonly associated with schizophrenia.\(^{[84][85]}\)

Dopaminergic dysregulation has also been linked to depressive disorders.\(^{[86]}\) Early research in humans used various methods of analyzing dopamine levels and function in depressed patients. Studies have reported that there is decreased concentration of tyrosine, a precursor to dopamine, in the blood plasma,
ventricular spinal fluid, and lumbar spinal fluid of depressed patients compared to control subjects.\cite{87} \cite{88} One study measured the amount of homovanillic acid, the major metabolite of dopamine in the CSF, as a marker for the dopamine pathway turnover rate, and found decreased concentrations of homovanillic acid in the CSF of depressed patients.\cite{89} Postmorndem real time reverse transcriptase-polymerase chain reaction (RT-PCR) has also been used to find that gene expression of a specific subtype of dopamine receptor was elevated in the amygdale of people suffering from depression as compared to control subjects.\cite{90}

The action of commonly used antidepressant drugs also has yielded information about possible alterations of the dopaminergic pathway in treating depression. It has been reported that many antidepressant drugs increase extracellular dopamine concentrations in the rat prefrontal cortex\cite{91}, but vary greatly in their affects on the striatum and nucleus accumbens.\cite{92} \cite{93} This can be compared to electro convulsive shock treatment (ECT), which has been shown to have a multiple fold increase in striatal dopamine levels in rats.\cite{94}

More recent research studies with rodents have found that depression-related behaviors are associated with dopaminergic system dysregulation.\cite{95} In rodents exposed to chronic mild stress, decreased escape behavior and decreased forced swimming is reversed with activation of the dopaminergic mesolimbic pathway.\cite{96} Also, rodents that are susceptible to depression-related behavior after social defeat can have their behavior reversed with dopamine pathway activation.\cite{97} Depletion of dopamine in the caudate nucleus and nucleus accumbens has also been reported in cases of learned helplessness in animals. These symptoms can be reversed with dopamine agonists and antidepressant administration prior to the learned helplessness protocol.\cite{98}

### Therapeutic use

Under the trade names Intropan, Inovan, Revivan, Rivimine, Dopastat, and Dynatra, dopamine, as well as norepinephrine and epinephrine, are also used as pharmaceutical drugs in injectable forms in the emergency clinical treatment of severe hypotension and/or bradycardia, circulatory shock, and cardiac arrest, the latter of which for the purpose of cardiopulmonary resuscitation.\cite{99} \cite{100}

Levodopa is a dopamine precursor used in various forms to treat Parkinson's disease and dopa-responsive dystonia. It is typically co-administered with an inhibitor of peripheral decarboxylation (DDC, dopa decarboxylase), such as carbidopa or benserazide. Inhibitors of alternative metabolic route for dopamine by catechol-O-methyl transferase are also used. These include entacapone and tolcapone.

### Nonneural functions

#### Renal and cardiovascular

Dopamine (brand name Intropin or Giludop) also has effects when administered through an IV line outside the central nervous system. The effects in this form are dose dependent.

- Dopamine induces natriuresis (sodium loss) in the kidneys, and has a diuretic effect, potentially increasing urine output from 5 ml/kg/hr to 10 ml/kg/hr.\cite{101} \cite{102} Dosages from 2 to 5 μg/kg/min are considered the "renal dose".\cite{101} It was once thought that at this low dosage provided increased renal perfusion in critically ill patients. The mechanism was thought to involve dopamine binding D_1 receptors, dilating blood vessels, increasing blood flow to renal, mesenteric,
and coronary arteries, which would thus increase overall renal perfusion. However, recent multicenter, randomized trials have shown that this is not clinically effective. Thus, "renal dose" dopamine is largely considered a myth that has been propagated in medicine for the past 30 years.

- Intermediate dosages from 5 to 10 μg/kg/min, known as the "cardiac dose", additionally have a positive inotropic and chronotropic effect through increased β₁ receptor activation. Dopamine is used in patients with shock or heart failure to increase cardiac output and blood pressure. Dopamine begins to affect the heart at lower doses, from about 3 μg/kg/min IV.

- High doses from 10 to 20 μg/kg/min are the "pressor dose". This dose causes vasoconstriction, increases systemic vascular resistance, and increases blood pressure through α₁ receptor activation, but can cause the vessels in the kidneys to constrict to the point that urine output is reduced.

**Immunoregulatory**

Dopamine acts upon receptors present on immune cells, with all subtypes of dopamine receptors found on leukocytes. There is low expression of receptors on T lymphocytes and monocytes, moderate expression on neutrophils and eosinophils, and high expression on B cells and natural killer cells. The sympathetic innervation of lymphoid tissues is dopaminergic, and increases during stress. Dopamine can also affect immune cells in the spleen, bone marrow, and blood circulation. In addition, dopamine can be synthesized and released by the immune cells themselves.

The effects of dopamine on immune cells depend upon their physiological state. While dopamine activates resting T cells, it inhibits them when they are activated. Disorders such as schizophrenia and Parkinson's disease, in which there are changes in brain dopamine receptors and dopamine signaling pathways, are also associated with altered immune functioning.

**Toxicity**

The LD₅₀, or dose which is expected to be lethal in 50% of the population, has been found to be: 59 mg/kg (mouse; administered i.v.); 950 mg/kg (mouse; administered i.p.); 163 mg/kg (rat; administered i.p.); 79 mg/kg (dog; administered i.v.).

**In plants**

**Fruit browning**

Polyphenol oxidases (PPOs) are a family of enzymes responsible for the browning of fresh fruits and vegetables when they are cut or bruised. These enzymes use molecular oxygen (O₂) to oxidise various 1,2-diphenols to their corresponding quinones. The natural substrate for PPOs in bananas is dopamine. The product of their oxidation, dopamine quinone, spontaneously oxidises to other quinones. The quinones then polymerise and condense with amino acids and proteins to form brown pigments known as melanins. The quinones and melanins derived from dopamine may help protect damaged fruit and vegetables against growth of bacteria and fungi.

**Anti-herbivore**

Dopamine is released by the marine alga Ulvaria obscura as an anti-herbivore defense mechanism.

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We Can't Stop the Dopamine

Author Louann Brizendine, M.D., says:

Researchers at Stanford University showed that playing Wii activates parts of the male brain linked to dopamine production. Boys get rewarded by this feel-good brain chemical, just as they do when roughhousing. The more opponents they conquer, the more stimulated their male brain becomes, and the more dopamine their brains release. It's a thrill a minute.