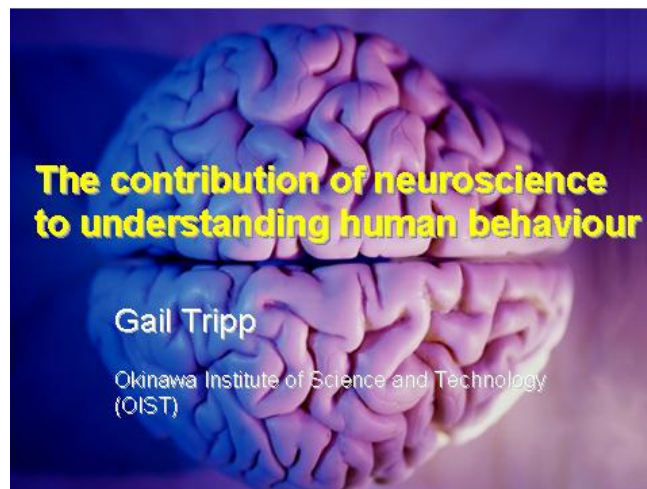


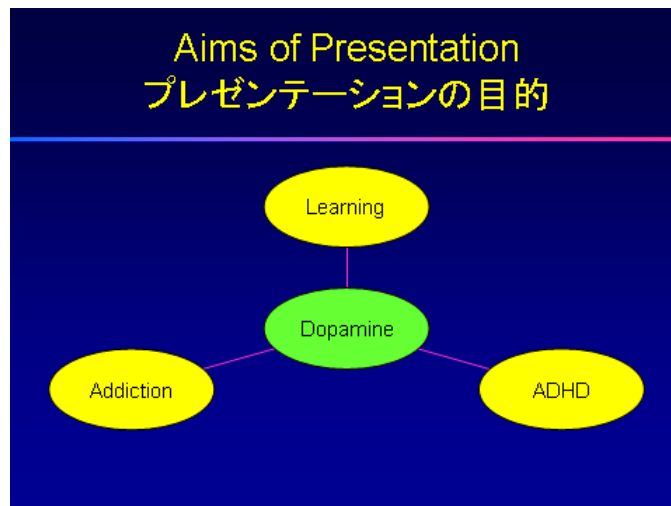
The Contribution of Neuroscience to Understanding Human Behaviour

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Today I want to illustrate the contribution that neuroscience is making to our understanding of normal and disordered human behaviour by considering what neuroscience research has taught us about

The biological basis of how we learn

Possible mechanisms of addiction

Biological explanations for attention deficit hyperactivity disorder (ADHD).

These three examples are linked by the common involvement of a brain neurochemical, dopamine.

Costs of Abnormal Behaviour: Addiction 異常行動のコスト：依存

	<p>Individual Impaired physical, social, and occupational functioning</p>
	<p>Family Negative impact on family and significant others</p>
	<p>Societal Financial costs, law and order, community</p>

The importance of neuroscientific understanding is easily appreciated by considering the negative impact of addiction and ADHD, as examples.

Pathological behavior has costs to the individual, family and society.

Addiction. At the individual level addiction leads to impaired physical, social and occupational functioning. It may lead to divorce, crime, incarceration and even death. These have negative impacts on the individual's family and significant others. At the societal level the costs can be

measured in terms of financial costs, negative impact on law and order, and negative impacts on whole communities.

Costs of Abnormal Behaviour: ADHD 異常行動のコスト: 注意欠陥多動性障害



Individual
Impaired behavioural, educational and/or occupational, and social functioning



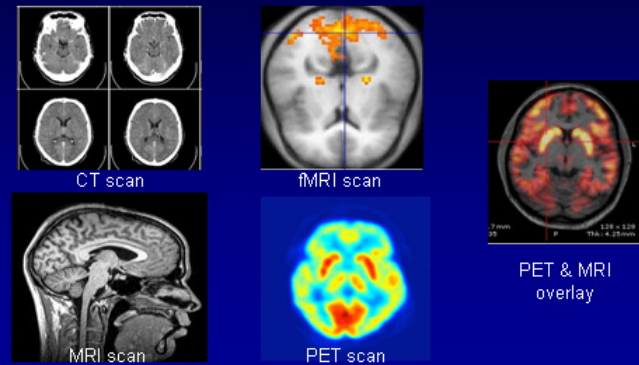
Family
Parental stress, caregiver burden, social isolation, occupational functioning

Societal
High financial costs (e.g., lost job productivity, increased health care)

ADHD. At the individual level ADHD leads to impaired behavioral, educational/occupational and social functioning. At the family level there is parental stress, caregiver burden, social isolation, and negative impact on occupational functioning. At the community level there is a financial cost in terms of lost job productivity and increased health care.

Neuroscience has the forward goal of better understanding of such disorders, and their diagnosis, treatment and prevention. There is potential to treat disorders by development of new drugs and psychological therapies. A better understanding of the mechanisms can help us to understand individuals who have such disorders, and to respond effectively. Accurate diagnosis is helpful even if there is no treatment.

Progress in neuroscience – brain scans 神経科学における前進 – 脳画像



CT scan

fMRI scan

MRI scan

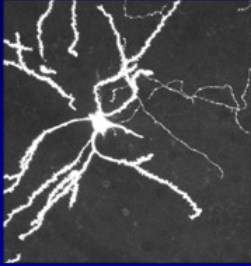
PET scan

PET & MRI overlay


Neuroscience is a relatively new discipline that is really a combination of the many different approaches needed to understand the brain. It certainly has few answers at the present time, but it is in a phase of rapid advancement. We have already seen a shift from describing brain structure to explaining brain function, made possible by remarkable technical and theoretical developments. As

we shall see later in the talk, observation of the living brain is very difficult because of the small size and fine structure of its cells. Until recently it was only possible to observe dead tissue. This allows study of fixed structure, which gives a snapshot in time, but does not reveal the function of the tissue.

The Scale of the Brain 脳のスケール



A neuron magnified 1000 times
There are about 1 million (100 万)
neurons in the volume of a grain
of rice.



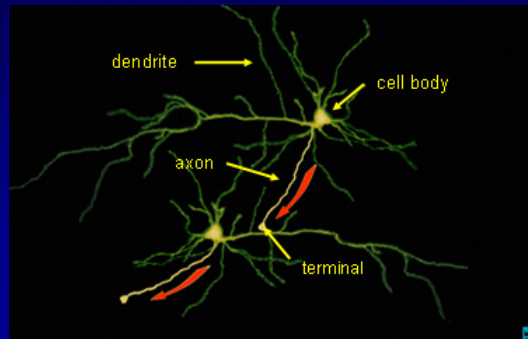
Tokyo rush hour

The total number of cells in the cortex is
1000 x population of Tokyo.
Each cell communicates with \approx 10,000
others.

Modern imaging methods allow study of the living brain. Using these methods we can begin to make measurements during such processes as learning and decision making and better understand the functions of the brain. This is a developing field and there are many limitations on our power of observation. For example we can measure which parts of the brain are active on a scale of a few millimeters, but the same techniques cannot be used to measure small cells or networks. Increased spatial resolution, faster imaging, and the ability to detect the activity of specific molecules is becoming available with new techniques, drawing on advanced physics, chemistry, and molecular biology technologies. However, these have a long way to go. Also, it is not only the ability to measure that limits us, but also the complexity and scale of the brain. For comparison, Tokyo has about 10 million people. Imagine the difficulty of tracking the communication of all of these people during the day. Now consider the total number of cells in the cerebral cortex is 1,000 times the population of Tokyo, and each cell communicates with about 10,000 others. The scale of the brain is astronomical.

Neurons are excitable cells that produce electrical signals

ニューロンは電気信号を伝える



The fundamental unit of the brain is the nerve cell or neuron. This slide shows two neurons. The central bright region in the neuron's cell body, which contains the cell's DNA and machinery to keep it alive and support its functions. The dendrites are the thick processes that radiate out from the cell body. They receive inputs from other cells and combine the information. Neurons are excitable cells that produce electrical signals called the nerve impulse. The nerve impulse is transmitted from the cell body to other neurons by the axon, which is the fine process connecting the two cells shown. The neuron is the basic computational element of the brain and combines its inputs to compute an output. The communication point between neurons is the synapse.

Synapse
シナプス
x 100,000

The connections
between neurons are
called synapses.

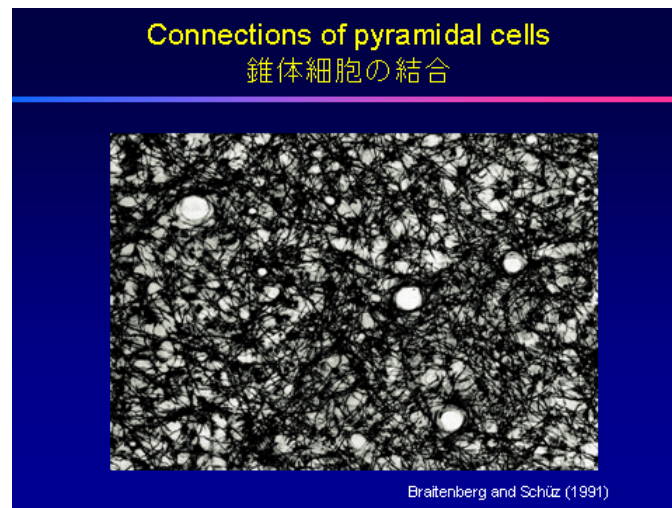
There are about
10,000 synapses on
each neuron



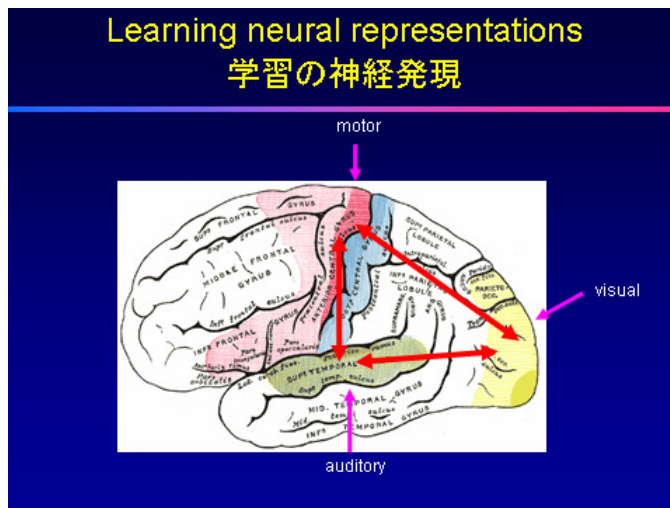
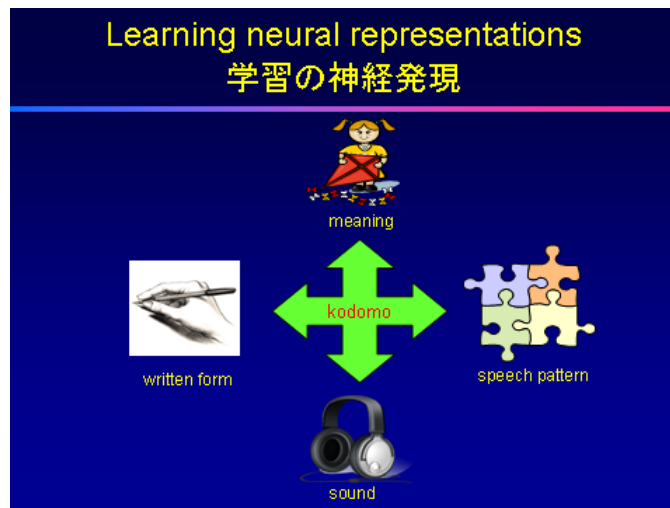
Image by Graham Johnson

This slide shows a single synapse. There are about 10,000 synapses on each neuron in the cerebral cortex. The synapse is the point of connection between neurons, but there is a small gap. The signal that crosses this gap is chemical rather than electrical. Different chemicals, called neurotransmitters, are used by different synapses. They are released from the nerve terminal and act on special molecules on the dendrites called receptors. They may activate or inhibit the next cell. Excitatory neurotransmitters such as glutamate make neurons more likely to fire. Inhibitory neurotransmitters such as GABA decrease the probability of firing. Later we will describe other types of chemicals that act at synapses, called neuromodulators.

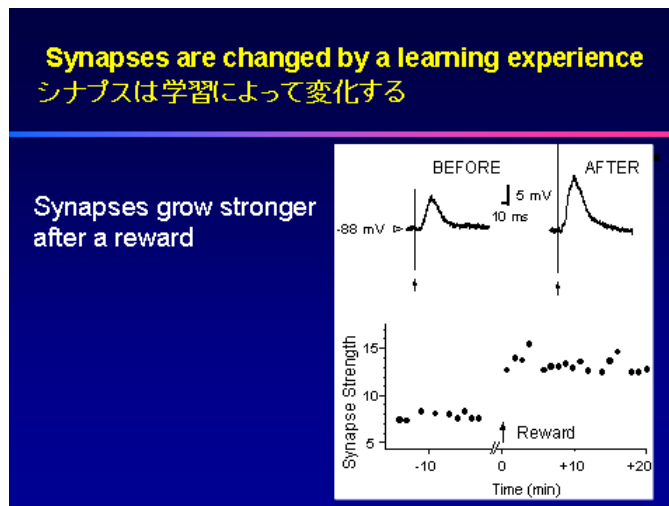
Firing is the propagation of the electrical signal to the next neuron, in other words, it is the way neurons communicate with each other. It usually requires excitatory inputs from several hundreds of synapses to fire a cell. The combination of the excitatory and inhibitory inputs is the fundamental basis of computation by the brain. However, a single neuron functions as a member of a larger neural network.



The degree of connectedness of the brain is astounding. In the cerebral cortex each neuron makes about 20,000 synapses, very few of which are with the same neuron. In some brain areas there are cells that have as many as 300,000 synapses. If we look at a picture showing the connecting axons, we see a dense network. From these observations we are impressed by the amount of connections. It has been suggested that the cortex is a connection machine. Why do we need so many connections? It is thought that ideas are represented in the cortex by combinations of active neurons. Perhaps by selecting connections we can make associations and form the substrate of ideas. However, the slide shows an example of fixed tissue. We can see the structure but can't figure out how it works without seeing the activity. Recently it has become possible to visualize the activity of the cells through the use of special dyes, combined with advanced microscopic techniques. Even then, we can see patterns of activity but we can't decipher its meaning. It has been suggested that the activation of a number of neurons together corresponds to "having an idea". But, where do the ideas come from? How do the connections form between the appropriate neurons? This raises the question of how we learn.

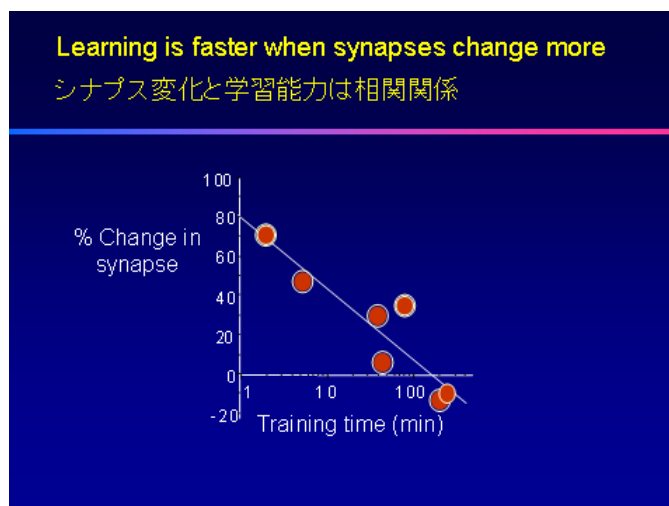


For many years it has been thought that learning involves changes in the synapses, thus making and breaking connections between nerve cells. This can change the likelihood that a certain group of cells can fire each other. For example, when you learn a new word in a foreign language, it has a certain sound, a written form, a speech pattern, and one or more meanings. E.g. kodomo. One has to hear and use the word many times before all of these aspects are brought to mind at once. This process may involve strengthening the connections between visual, auditory, motor, and association areas of the brain where the concept of a child, or children in general, is represented. Repetition seems somehow to stamp in the connections required. But obviously, it is more than that. Words that have motivational significance for the user are often easier to recall. 子ども is easier for a parent to learn. For a child, perhaps おかあさん is an easier word to learn.



In the past few decades, direct measurements of the strength of synaptic connections has become possible. These show that an experience can lead to a physical change in the synaptic connections. Such changes can increase the probability that the nerve impulse is propagated from one cell to the next.

This slide shows the strength of the connection before and after a momentary learning experience. The connection is stronger after the experience. Over time, the strength of the connection remains increased, long after the momentary experience is over.



It has been shown that degree of such change is correlated with the time it takes to learn a new behaviour: evidence that changes in synaptic strength underlie learning.

This slide shows the association of the synaptic change and learning. As you can see, learning was faster when synapse change was greater. This is evidence that learning involves synaptic change.

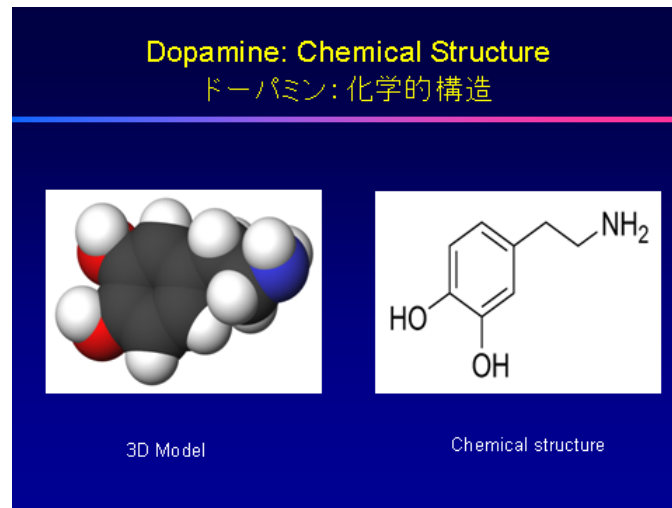
In the context of a network, this can lead to formation of a population of cells that fire together.

I have already mentioned the importance of motivation for learning. What is the neural basis of motivation, and how does it affect learning?

The answer to this question takes us back to the synapses and chemical synaptic transmission. Some neurotransmitters act differently from those we mentioned before. They act diffusely on many

neurons, more like hormones. Their effects are also different. Instead of simply exciting or inhibiting cells, they can change the sensitivity of the cell to other neurotransmitters. They act like a cellular volume control. These chemicals are called neuromodulators.

Neuromodulators are important in mediating emotional responses.



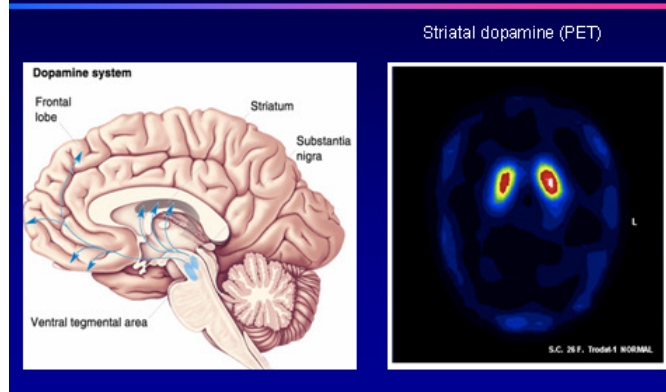
Dopamine is a very important neuromodulator. It has been associated with pleasurable events, and in the popular press, has been described as the pleasure molecule. Certain emotional experiences cause the release of dopamine. During learning, dopamine is released in the brain. It is released in response to positive events such as food, water, and sex. These events are very significant for the organism, not least because they are essential for life. Moreover, such events are memorable. What is the connection between dopamine, pleasure, and learning?

Neuroscience has discovered that dopamine, like other neuromodulators, can act on synapses and reinforce the effects of experience. The action of dopamine is to facilitate learning by enabling synaptic change to occur.

Neuroscience research has shown that dopamine is released not simply by pleasurable events. Dopamine is released when an action produces a positive outcome. Over time, dopamine comes to be released in anticipation of positive outcomes. It is thought that the anticipatory release serves to make behavior more adaptive. This is essential because positive outcomes are often delayed. For example, we work every day, but only get paid once a month. What keeps us working when we are not being paid? We believe it is the release of dopamine in anticipation of payment, and this anticipatory dopamine maintains our working behavior.

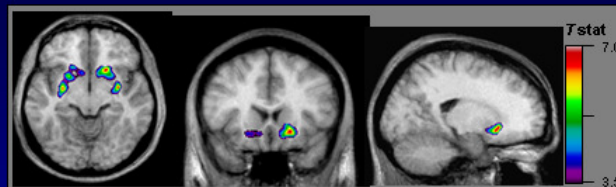
When the dopamine system malfunctions

ドーパミンシステムの機能不全

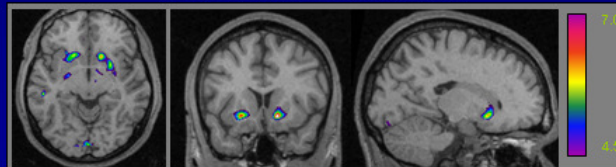


PET studies of drug addiction 薬物依存患者のPET画像

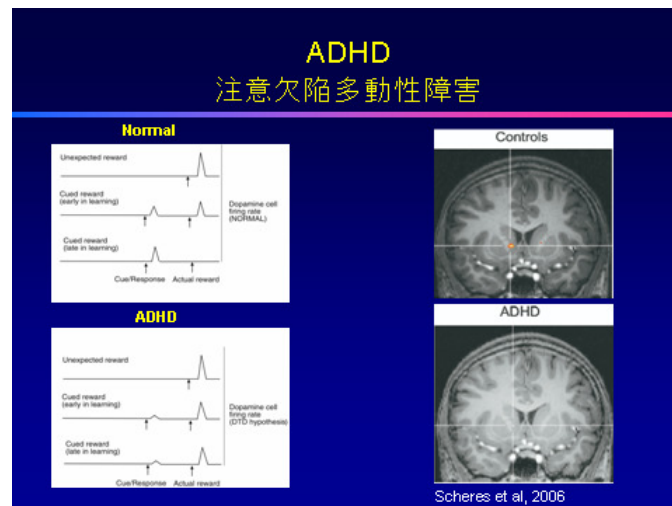
Amphetamine-induced dopamine release



Alcohol-induced dopamine release

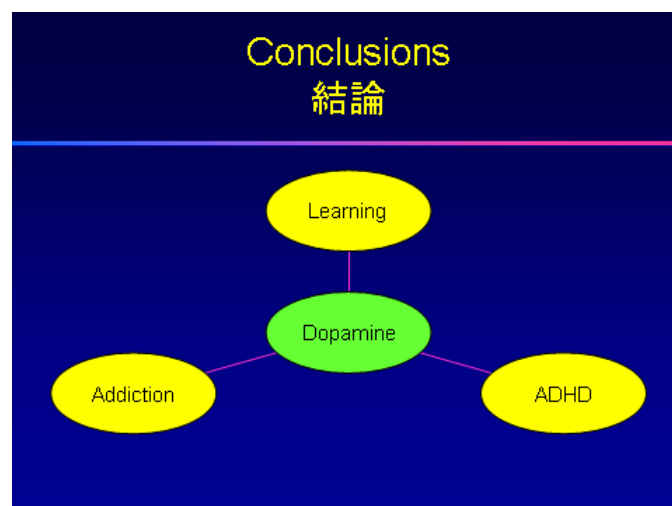


Although there are many different drugs of abuse, and these have different chemical structures, many of them have in common the ability to mimic the action of dopamine. In addition to any positive feelings the drug may produce, the dopamine-like action strengthens the drug-taking behavior. It is thought that the mechanism of addiction may involve hijacking of the brain's normal learning mechanism. The drugs facilitate learning of drug taking behavior by physically changing synapses in the brain. Understanding this can change the way we think about drug addicts. For example, the way the brain works when an addict chooses to take a drug is different from the way it works when a non-addict takes a drug. The question arises whether the addict continues to have a choice.



ADHD is common and disabling disorder. The symptoms of ADHD are developmentally inappropriate levels of inattention, overactivity and impulsivity which impair the individuals functioning. The neural mechanism for ADHD is not known.

In ADHD behavioral research has demonstrated abnormal sensitivity to the positive outcomes of actions. This has led to much speculation that altered brain mechanisms for reinforcement underlie many of the symptoms of ADHD. Our speculation is that abnormal operation of the dopamine system is important in ADHD. We are suggesting and preparing to test the hypothesis that the anticipatory release of dopamine is not occurring normally in ADHD. Already, there is some evidence for this from brain scans, which show less activation of certain parts of the brain in anticipation of positive outcomes in the brains of adolescents with ADHD. Further study of the mechanisms underlying ADHD is a future challenge for neuroscience.



I hope I have managed to convey to you the scale and complexity of the problem facing neuroscience. We have learnt much in recent years, but there is a great deal waiting to be discovered. We have already uncovered crucial parts of the brain's learning mechanisms at the level of the synapses and neurotransmitters. We are starting to appreciate the importance of neuromodulators in normal learning and abnormal behavior such as addiction and ADHD. As neuroscience progresses

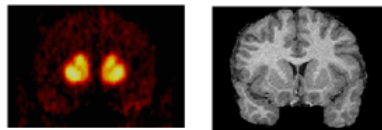
we can look forward to improvements in understanding, treatment, and hopefully prevention of these and other important disorders.

Image acknowledgements

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MRI – Wikipedia (Eric 1980)
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PET/MR – Wikipedia (Mco44)
Neuron – BAM_school, SFN
Dopamine molecule – Wikipedia (Harbin)
Drug addiction PET scans. L. S. Kegeles, W. G. Frankle, D.-R. Hwang, Y. Huang, E. Hackett, S. Curry, A. Abi-Dargham, and M. Laruelle. Division of Functional Brain Mapping, New York State Psychiatric Institute, Departments of Psychiatry and Radiology, Columbia University, NY

GABAergic modulation of subcortical dopamine release in healthy humans measured by [¹¹C]raclopride PET



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