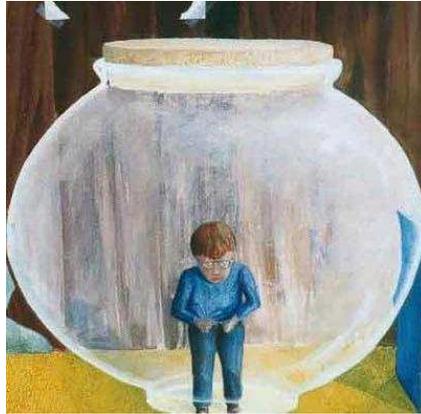


## Shut off



Autism has its ways. We have all seen someone brushing against a wall, blatantly avoiding eye contact or shunning dialogue like the plague. What may seem like an extreme form of shyness to some is in fact a means of protection against a world that cannot be apprehended the way most of us do. A wall is reassuring, avoiding eye-contact is protective and silence is a shield. Autism is a syndrome - with more or less severe characteristics - that isolates those suffering from it into a world of their own, though some forms do conceal unexpected and surprising personalities. What causes this illness is still poorly understood, but it is now clear that the complex factors at the root of it include both the environment and proteins in the brain.

### *A question of solitude*

*Rain Man*, the main character of the well-known film that came out in the 1980s, could tell how many matchsticks had fallen on the floor in a matter of seconds. Dustin Hoffman played the part very aptly and his moving portrayal brought autism to the public's notice. Behind it all, Kim Peek - whose story inspired the film - is the 'real' Rain Man and is still alive today. Despite language and behavioural disorders, Kim Peek is considered to be "of high intellect" and presents extraordinary intellectual faculties, namely in mental arithmetic.

There are many types of autism and, like the colours on a painter's palette, the degrees of severity of the symptoms are infinite. Nevertheless, this disconcerting pathology invariably occurs in three distinct behavioural spheres: human interaction, verbal and non-verbal communication, and fields of interest.

People suffering from autism are generally described as being self-absorbed: they avoid eye contact and seem indifferent to things and people around them. They are unable to make conversation but repeat words or phrases that have just been said. Metaphors, such as 'a slap in the face' are beyond them because they tend to take them literally. Their lack of empathy for others is yet another social hurdle although they are capable of emotions such as fear and pleasure.

Despite all this, they pay a disproportionate attention to detail. Their unwavering interest in meteorological bulletins or train timetables is simply a way to shy away from human interaction, and the resulting emotions, that could engulf them like a tidal wave. Withdrawal not only reveals their difficulty to relate to others and express themselves, but it also seems to be the only way they have to fend off any source of anguish and emotional upheaval.

---

### Kim Peek's memory

---

*The "real" Rain Man was born in 1951 in the United States of America. Kim Peek has a photographic memory, which could almost be qualified as 'absolute' because it is so true to reality and seemingly unlimited. Before he could walk, he had already stored in his mind all kinds of information. Today, he has memorized over 9'000 books on subjects as varied as music, astronomy, history and literature. Furthermore, he is capable of amazing feats in mental arithmetic, an ability shared by many other autistic people of his kind.*

---

Another distinctive sign of people with autism are the bodily attitudes they adopt, which often betray their inner agitation and anxiety. They are often seen lost in repetitive movements, rocking themselves backwards and forwards for example, touching door handles or even hitting their heads against a wall. There are many more symptoms: a complete lack of imagination and fantasy, the inability to imitate the actions of others, a hypersensitivity to outer stimuli such as certain sounds and a deep-rooted resistance to change.

#### ***A belated discovery for a precocious pathology***

Autism is derived from the Greek "autos" which means "self", and underlines the main characteristic of autism: self-absorption. Historically, 'autism' was not used to define a condition such as Kim Peek's. Eugen Bleuler, a Swiss psychiatrist, first made use of the term in 1911 to refer to the central symptom of schizophrenia: "withdrawal into oneself".

Reference was made to autism in the early 1940s when Leo Kanner, an American psychiatrist, and Hans Asperger, an Austrian psychiatrist, reintroduced the term to identify this unique pathology. Independently, the two psychiatrists discovered the precocious disorder, which affects five children in one thousand and about three times more boys than girls.

Although some kind of autism may be suspected in a child's very early years, it is usually not possible to give a reliable diagnosis before the age of three. The earlier the syndrome is diagnosed the better, since a child can benefit from a specialised education because, sadly, there is no cure for autism. In this respect, nowadays, people suffering from autism can take advantage of several therapies. Such therapies can help them to adjust their social behaviour, develop non-verbal communication or teach them how to be autonomous - all of which aim to breach the wall that shuts them off from those closest to them and the world around them.

#### ***A puzzling origin***

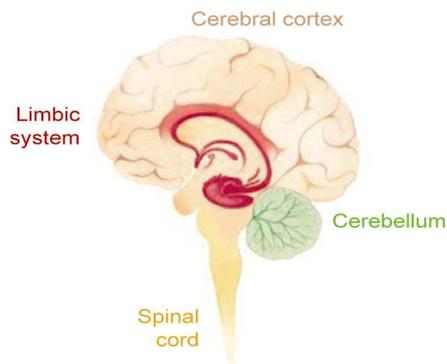
When, in the 1950s, autism was beginning to draw attention, psychoanalysis was in its heyday and putting many psychiatric disorders down to difficult parent/child relationships. Autism was no exception, and its origin was attributed to a maladjusted relationship between a mother and her child. And some American doctors went so far as to recommend their separation.

What can be the cause of autism? Why are there so many degrees of severity in the symptoms? Both the progress made in medical analyses and extensive knowledge acquired on the brain have given rise to many theories. Although no one has reached the crux of the matter, researchers believe there are many causes - such as illnesses that present an autistic trait, environmental factors and genetic anomalies.

The study of other pathologies has revealed that the symptoms known to be characteristic to autism are not necessarily specific to it alone. Rett's syndrome for instance, that affects only girls, is characterized by an autistic state accompanied by the loss of speech, and is the result of a modification in a single protein. Furthermore, women who have one X chromosome instead of two and who thus suffer from Turner's syndrome which affects their genital organs (read also "♂ or ♀: that is the question", issue March 2007) are more liable to develop an autistic trait, although the reason is not clearly understood.

And environmental factors? Towards the end of the 1990s, rumours of the possible danger of vaccines were beginning to spread. They first arose when children who had been vaccinated against measles, mumps and German measles allegedly developed autism. There was a general uproar, but a few years later all doubt was lifted when it was shown that the results of the analyses had been distorted. Since then, the vaccine's responsibility has been completely cleared. However, other environmental factors have been demonstrated to have a role in autism. As an example, if the cytomegalovirus - the virus responsible for German measles - is contracted

during pregnancy, the child can develop a form of autism.



**Fig.1** The affected zones of an autistic brain seem to be the cerebral cortex, the limbic system and the cerebellum.

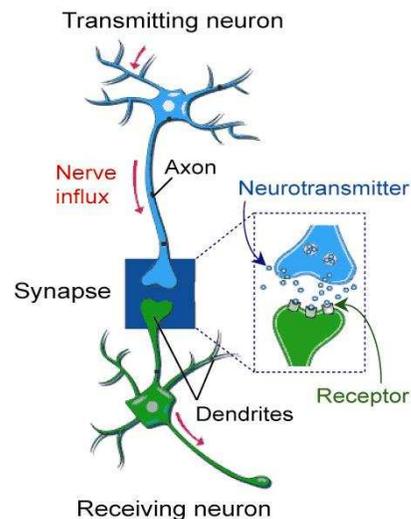
As for the genetic factors, their number is ever growing. Most of them are genes and proteins involved in the development of the brain. There is no doubt that autistic symptoms are brought on by the dysfunction of certain cerebral regions. (fig.1). Since autism is characterised by deep anxiety, language difficulties and social withdrawal, it is greatly suspected that interactions between the limbic system and the cerebral cortex are impeded. The limbic system is part of the central nervous system associated with emotions, voluntary movement and sensory sensitization, while the cortex deals with language, learning and behaviour.

### Communicative proteins

Among the proteins suspected of being involved in autism, many are involved in neuron-to-neuron communication, which is an essential function of the brain, and located in what is known as synapses. A synapse is the region where two neurons make contact - one emits a message while the second receives it. In order to transmit information, neurons use two types of cellular prolongation that act as communicating organs. The emitting neuron sends a message through a sort of cable - its axon - and the receiving neuron picks it up thanks to an antenna: a dendrite (fig.2). Both the axon and the dendrite constitute what is known as the synapse. Their mere existence, however, is not sufficient. Besides the axon/dendrite pair, neuronal communication demands a host of proteins such as receptors, adhesion molecules and assembling proteins.

The receptors are proteins located on the surface of dendrites. Their specific role is to relay information to the inside of the receptor neuron. How? The emitting neuron discharges

chemical molecules, known as neurotransmitters, through the terminal ends of its axon. These neurotransmitters cross the synaptic cleft and are collected by specific receptors placed at the terminal ends of the dendrites. There are several types of receptor and each is defined by the neurotransmitter it recognizes. In this way, the GABA and glutamate receptors - the two largest groups in the brain - recognise GABA and glutamate, respectively. What information do GABA and glutamate receptors relay? GABA receptors send a no-go signal whereas the glutamate receptors give a go-ahead signal, and the message is transmitted to another neuron.



**Fig.2** The structure of a synapse. The emitting neuron transmits the message by way of nerve impulses along its axon. These impulses are then relayed by neurotransmitters in the synaptic cleft, which are picked up by receptors on the dendrites' surface. The message is then dealt with by the receiving neuron.

Transmission across a synapse involves a form of "intimacy" between neurons. The synaptic contact is made thanks to what is known as adhesion proteins. In several cases of autism, two of such proteins - neuroligins 3 and 4 - have been found at fault as a result of a modification in their genes. Under normal circumstances, neuroligins 3 and 4 are embedded in the dendrite's membrane and they "cling" to other adhesion proteins on the axon facing them. However, if they are modified one way or another, these neuroligins are inoperative. Scientists believe that this could be the cause of synapses that haven't been able to form and, as a result, neuronal communication is disrupted. In the long run, the lack of certain synapses could alter the function of the cerebral structures that have been affected.

---

### Stephen Wiltshire, autistic artist

---

*Although a talented musician, Stephen Wiltshire has become a brilliant draughtsman. English and born in 1974, he lost all faculty of speech at the age of 3 after his father died. Diagnosed an autistic child, he was sent to a specialised school and very quickly showed a fascination for shapes and images. He began to "doodle", drawing mainly cars, then buildings, and showing an acute sense of perspective. (cf. fig.3). Like Kim Peek's, his visual memory is photographic. He needs no sketch or outline to reproduce without hesitation the smallest of details in a building, a street or even a city such as Rome. He is now a well-known artist and his work is shown in galleries throughout Britain and the United States of America.*

---

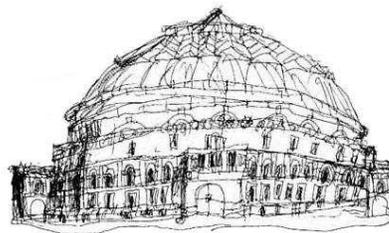
In autism, the neuroligins and the glutamate receptors in the dendrites have a common partner: an assembling protein named Shank3. An "assembling protein" is a bit like an adaptor around which proteins form a kind of scaffold. Shank3 has a specific helical region called SAM, where it can "auto-assemble", i.e. it is able to associate with a vast number of proteins, in particular with the neuroligins and glutamate receptors. Shank3 can also bind to the receptors' partners which deal with signal transduction, as well as to the cytoskeleton, the network of proteins which forms a dendrites' morphology. Hence, the role of Shank3 is crucial not only in the formation of dendrites and their correct function but also, in passing, in that of the synapses. Consequently, as it has recently been observed in autism, a dysfunctional Shank3 could be the cause of a deficiency in neural communication - which is one of the causes of the pathology.

#### **Exceptional autism**

Although autistic individuals find it extremely difficult to relate to other people - which, in turn, has perplexing consequences for their neuronal system - a few do develop exceptional talents. About 10% are what used to be called "learned idiots" or "prodigies" and, today, they are known as patients with "high standard autism". Many are famous, such as Kim Peek with his photographic memory and the film he inspired - *Rain Man* - and Stephen Wiltshire for his graphic talent in reproducing urban scenes.

Among the extraordinary autistic people, a number suffer from Asperger's syndrome. This particular syndrome was first described in 1944 by the Viennese psychiatrist Hans Asperger but only recognized in 1981 because of the lack of a translation of his work, until then only published in German. There is a difference between autism and Asperger's syndrome, however though there is no clear explanation to date. The "aspergers" or the "aspies", as they are called, are of standard intelligence or even slightly more intelligent than the norm. The majority show no signs of language-

learning in their infancy, as in other forms of autism, and are able to share their experiences, their feelings and their emotions with others. However, they still reflect the most characteristic trait of autism: a more or less pronounced inability to socialise.



**Fig. 3** *The Royal Albert Hall in London, drawn by Stephen Wiltshire at the age of 9.*

Born in the United States in 1947, Temple Grandin was initially diagnosed with autism. However, with time, her doctors now believe she suffers from a form of Asperger's syndrome. Her family has been a family of farmers for generations, and Temple developed a passion for animals from a very early age. She quite naturally took on veterinary studies and, in time, was appointed professor at the University of Colorado. Moreover, particularly mindful of animal well-being, she became involved in the design of cattle equipment and is today an expert in the field. Conscious both of her pathology and its failings in her make-up - such as the misunderstanding of human interaction like the use of metaphors, and her difficulty to form emotional bonds with fellow humans - Temple Grandin has been sharing her experience of autism with the public at large, and wrote *My Life with Autism*, an autobiography and a unique record of its kind.

Despite their exceptional life stories, people like Temple Grandin, Tim Peeks and Stephen Wiltshire are still deeply affected by their illness and it would be wrong to minimize their relational and emotional difficulties, which are a severe handicap in their social lives and autonomy. While fascinating for some and disturbing for others,

their stories make us marvel. How can failings in the brain bring about such talents? How is it possible to survive in such social and emotional isolation? If research into the world of autism questions our inbred perception of social

normality, it also reminds us that we are still far from unveiling the intricacies of the human brain.

Séverine Altaïrac\*

\*Translation: Geneviève Baillie

### ***For further information***

#### **On autistic artists:**

- Kim Peek, the "real" *Rain Man*:  
[http://en.wikipedia.org/wiki/Kim\\_Peek](http://en.wikipedia.org/wiki/Kim_Peek)
- Stephen Wiltshire, city drawer:  
<http://www.stephenwiltshire.co.uk/>
- Temple Grandin, professor and writer:  
<http://www.grandin.com/>
- Matt Savage, jazzman:  
<http://www.savagerecords.com/>
- Christophe Pillault, painter:  
<http://monsieur.wanadoo.fr/christophe.pillault/index.jhtml>
- Véronique Ferrandis, painter:  
<http://www.veroniqueferrandis.com/?page=main&lang=en>
- Zoe Kalkyris, painter:  
<http://www.zoes-world.co.uk/index.php>
- Cécile, poet:  
<http://web.telia.com/~u31231180/presentation.htm>

#### **On the Internet:**

- Autism:  
<http://en.wikipedia.org/wiki/Autism>

#### **A little more advanced:**

- A book recounting the story of people suffering from neurological troubles, amongst which autism : Oliver Sacks, "An anthropologist on Mars"
- The discovery of Shank3's role in autism: Durand C.M et al., "Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders", *Nat Genet.* 39:25-7(2007) PMID: 17173049

#### ***Illustrations:***

- Heading illustration, Source: [http://www.xs2-school.nl/Autisme\\_121.html](http://www.xs2-school.nl/Autisme_121.html)
- Fig.1, Adaptation: [http://fr.wikipedia.org/wiki/Syst%C3%A8me\\_limbique](http://fr.wikipedia.org/wiki/Syst%C3%A8me_limbique)
- Fig.2, Adaptation: [http://www.droques.gouv.fr/fr/savoir\\_plus/livrets/action\\_droques/action\\_page2.html](http://www.droques.gouv.fr/fr/savoir_plus/livrets/action_droques/action_page2.html)
- Fig.3, Source: [http://www.stephenwiltshire.co.uk/art\\_gallery.aspx?Id=144](http://www.stephenwiltshire.co.uk/art_gallery.aspx?Id=144)

#### ***At UniProtKB/Swiss-Prot:***

- Neuroligin-3, Homo sapiens (human): Q9NZ94
- Neuroligin-4, Homo sapiens (human): Q8NOW4
- Shank3, Homo sapiens (human): Q9BYB0

*Date of publication: June 12, 2007*

*Date of translation: June 12, 2007*

---

Protéines à la "Une" (ISSN 1660-9824) on [www.prolune.org](http://www.prolune.org) is an electronic publication by the Swiss-Prot Group of the Swiss Institute of Bioinformatics (SIB). The SIB authorizes photocopies and the reproduction of this article for internal or personal use without modification. For commercial use, please contact [prolune@isb-sib.ch](mailto:prolune@isb-sib.ch).