Development of GABAergic neuron connectivity in health and in disease

The biological processes associated with neurodevelopmental disorders and diseases of the brain are still in part to be ascertained. Drs Graziella Di Cristo and Bidisha Chattopadhyaya, two scientists working at the Sainte-Justine hospital research centre, affiliated to the Université de Montréal, have conducted extensive research exploring brain development. Their latest work investigates the role of GABAergic neurons in brain disorders, including intellectual disability, autism and epilepsy. Drs Di Cristo and Chattopadhyaya use cutting-edge high-resolution imaging and gene manipulation techniques to gain insight on how disturbances in GABAergic circuits could lead to disruptions in cognitive function.

The brain is one of the most complex organs in the body, made of millions of neurons that communicate to each other through connections called synapses. To facilitate studies on such a complex biological network, neurons have been classified based on the neurotransmitters they release. In the mammalian neocortex, excitatory neurons that release glutamate predominate, but they are precisely modulated by a heterogeneous population of neurons that release neurotransmitter GABA – the GABAergic neurons.

Drs Di Cristo and Chattopadhyaya’s research aims to gain a better understanding of GABAergic neuron development, plasticity and function. Their work also provides insight into the potential causes and biological dynamics of a number of disorders, including intellectual disability, epilepsy, autism and schizophrenia, which have been associated with dysfunctions or unusual development of the brain.

BRAIN PLASTICITY

Brain plasticity (from the Greek word ‘plastos’, which means ‘moulded’) can be defined as the ability of the brain to change and adapt throughout life. The human brain has been found to modify itself over time, adapting to changes within the body or in the external environment by forming new connections between brain cells. These connections are formed via synapses, structures that allow neurons to communicate, passing electrical and chemical signals to one another. For instance, the brain of someone who suffered from a stroke that caused paralysis in a given part of the body could later shift activity related to the paralysed area to a different location, making new connections to adapt to the change.

DISORDERS OF THE BRAIN: AUTISM AND EPILEPSY

Drs Di Cristo and Chattopadhyaya’s recent research investigates brain plasticity and function in individuals suffering from autism and epilepsy. Autism is a highly variable neurodevelopmental disorder that first appears during infancy or childhood, and generally follows a steady course without remission. A lifelong disability, it affects how people perceive the world and interact with others. It is characterised by impaired social interaction, impaired verbal and non-verbal communication, and restricted and repetitive behaviour. Although it is understood that autism affects information processing in the brain by altering how nerve cells and their synapses connect and organise, how this occurs is not well understood.

Epilepsy is a medical condition that affects the brain, causing affected individuals to have repeated seizures, the severity of which can vary from case to case. During these seizures, neurons have been found to trigger abnormal electrical impulses. In some cases, onset of epilepsy can be attributed to stroke or brain damage. However, in most cases the exact cause for the condition is hard to identify.

THE ROLE OF GABAergic NEURONS

Dr Di Cristo and Dr Chattopadhyaya investigate the role of GABAergic neurons in relation to brain disorders such as intellectual disabilities, autism and epilepsy. GABAergic neurons are cells that generate gamma aminobutyric acid (GABA), an inhibitory neurotransmitter within the central nervous system (CNS). GABA, a chemical used as a means of communication between neurons, helps to reduce excitation in the nervous system. GABAergic circuits have been found to control the function of cortical networks, regulating the development of the brain by moderating the proliferation and connectivity of neurons.

Irregular development of GABAergic circuits has been associated with a number of neurodevelopmental disorders, including schizophrenia, autism, and Tourette’s syndrome. Due to the complexity of the brain and its circuits, understanding how GABAergic neurons form synapses has so far been very challenging.

THE ROLE OF GABA IN BRAIN-RELATED DISORDERS

Both autism and epilepsy appear to be associated with defects in the development of GABAergic neurons, particularly in the GABAergic circuits have been found to control the function of cortical networks, regulating the development of the brain.
When did you start researching brain development and plasticity?

Dr Cristo: As an undergrad in Pisa, in 1995, I had the opportunity to work in the lab of Prof Lamberto Maffei, learning how to record visual cortical neuron activity to study mechanisms of brain plasticity, for example, what makes the brains of children more amenable to learning new things as compared to an adult, and this to me was such an exciting question to explore.

Chattopadhyaya: I was first exposed to the field of synaptic development and plasticity when I started my PhD with Dr. Joel Haudin in Cold Spring Harbor in 2000, where we were developing new genetic tools to label and manipulate different types of GABAergic neurons, with the aim of understanding if and how they may alter plasticity in the developing brain. Since GABAergic neurons are so heterogenous in the brain, there were no established techniques to reproducibly identify them then in live tissue, and it was just amazing when we could first consistently label them and could actually visualise how they form synapses/connections.

What do you feel are some of the greatest mechanisms related to the study of brain function and development?

There are many critical aspects in brain development, such as, how different types of neurons are generated, how they establish their identity, how they connect to each other, and in doing so form neural circuits that make a functional brain that is responsive and adapts to its environment. More recently, Drs Cristo, Chattopadhyaya and Michaud further explored the neural dynamics behind intellectual disabilities and autism, with a particular focus on the role of GABAergic circuits. Previous research by Dr. J. Michaud and other researchers has shown that GABAergic circuits are critical for the development of cognition and formation of synapses, with mutations of this gene potentially causing intellectual disabilities, autism and epilepsy. Together with Dr. Michaud, Dr Di Cristo and Dr Chattopadhyaya found that SynGAP1 gene mutations reduced the formation of connections between particular GABAergic cells. Such reduced inhibitory synaptic activity suggests that SynGAP1 mutations in GABAergic circuits could contribute to autism and related syndromes with neurodevelopmental disorders.

BREAKING THE BRAIN CODE

The dynamics of the human brain are incredibly complex, which makes the attribution of specific roles and functions to its different circuits a challenging task. Drs Di Cristo and Chattopadhyaya’s research has substantially contributed to the study of brain plasticity and development, with their most recent work suggesting that dysfunction in the developing GABAergic circuits is related to the cognitive deficits seen in individuals with disorders, such as intellectual disabilities, autism and epilepsy. In future, this could help to develop effective pharmacological treatments for these often debilitating conditions, which would counteract the chemical imbalances in the brain of those affected.