No filter

Dr Susanne Schmid harbours a longstanding fascination with the complex mammalian brain. Here, she explains how her research is tackling one of the major challenges in modern neuroscience: understanding how the brain processes sensory information to engender the appropriate behavioural response.

Why is sensory filtering so important and what are the potential implications for an individual when this mechanism fails to function normally?

Sensory filtering is vital because the brain constantly receives sensory information from our five senses and not all of it is important. There is a lot of repetitive information that we do not need to attend to and our brains have built-in mechanisms to filter out bits that are repetitive or unimportant. These mechanisms protect the brain’s resources and allow us to focus on salient information and suppress background noise. If our ability to repress this noise does not function normally then the brain is easily overloaded with information. As a result, it is difficult to focus attention and concentrate on specific aspects.

Can you summarise the symptoms of schizophrenia that are caused by a breakdown in sensory filtering?

The disruptions in sensory filtering do not only apply to schizophrenia but also to autism and a range of other mental disorders and neurodegenerative diseases. However, these symptoms are most prevalent in schizophrenia and autism. When sensory filtering does not work this impacts cognitive function, including the ability to learn, working memory and attention span. It is a matter of debate as to whether sensory filtering also plays a role in causing some of the positive symptoms of schizophrenia such as hallucinations and delusions.

To what extent do habituation and prepulse inhibition act as good measures of sensory filtering? Can you briefly explain these terms?

We measure sensory filtering in both humans and animals through a technique called the acoustic startle response, and examine the habituation and prepulse inhibition of that response. Habituation is when we attenuate our response to repetitive stimuli – a process that is deficient in patients with schizophrenia and autism. We also observe a disruption in prepulse inhibition as well, particularly in schizophrenia, but also Parkinson’s and Alzheimer’s disease to a lesser extent. Prepulse inhibition describes the fact that if there is a normal sensory stimulus that precedes the startle stimulus, the startle response will be greatly attenuated. The underlying concept is a little more complicated; put simply, it means that individuals with disrupted prepulse inhibition cannot focus their attention properly on something, they are more likely to become distracted and show improper behavioural responses.

Are there particularly unique or advanced methodologies that you use in your research you would like to elaborate on?

We do use some cutting-edge technologies. One of the most interesting is how we test attention and distractibility in our rats using a touchpad – similar to a tablet computer. We train the rats in boxes where we do a classical task called the Five Choice Serial Reaction Time task. During this, they initiate a trial by touching a spot at the back of the box with their noses causing a specific field on the tablet to light up 5 seconds later. They need to keep their attention focused for the 5 seconds and then touch this exact spot on the tablet. We can also give distracting noise during the attention period in order to see whether they can still maintain their focus. We do this with both normal and autistic rats. Another method we use is optogenetics. This involves novel technology in which we insert light sensitive ion channels into the synapses of cholinergic neurons and activate them by light.

You are in the process of shifting your focus from the context of schizophrenia to autism. How are the findings you have made to date, working on schizophrenia, applicable to the treatment of autism and other diseases?

Our work targets a group of symptoms that are common to both schizophrenia and autism. The reason for the shift towards autism is that it is very difficult to have a good animal model for schizophrenia because it is intrinsically a mental disorder; you can never tell if a rat is hallucinating or not. With autism, however, we have better rat models. We use a model where we give a prenatal injection of valproic acid – an antiseizure and antimigraine medication which, when taken by pregnant women, increases the risk of autism for their child – and these rats then display typical autism behaviours such as stereotypic movements, social behaviour deficits and learning disruptions.
FROM THE MOMENT we wake up until the moment we go to bed, our brains are constantly bombarded with an abundance of sensory information. Derived from our senses, the overwhelming majority of this information is filtered out before we are even conscious of it. This prevents the higher cortical centres of the brain from being overloaded with irrelevant data – and it is a pre-requisite for vital cognitive functions such as attention span, memory and social interaction. Yet, the reverse is also true; any disruptions in the body’s sensory filtering system have negative repercussions on higher cognitive functioning.

Unsurprisingly, problems with sensory filtering have long been associated with a number of mental and neurodegenerative diseases, particularly schizophrenia and autism. In the case of schizophrenia, patients are usually prescribed antipsychotic drugs; however, while these are highly effective at preventing hallucinations, they have a minimal impact on sensory filtering abilities. This means that many patients are unable to function normally at a cognitive level – and persisting memory, attention and social interaction deficits often prevent them from going back to work or from living a normal, well-adjusted life. There is, therefore, a compelling need for research that unveils the complex mechanisms of sensory filtering circuits, in turn paving the way for potential drug targets.

Drawing on their animal models of schizophrenia and autism, a team of researchers at the Schmid Lab – based in the University of Western Ontario’s Schulich School of Medicine and Dentistry – are attempting to respond to this need. Led by Dr Susanne Schmid, Associate Professor of Neurobiology and Associate Chair for Research in the Department of Anatomy and Cell Biology, these researchers are making promising strides in understanding the processes that underlie both normal and disrupted sensory filtering. Using two operational measures to explore these processes – namely, habituation and prepulse inhibition – they are primarily focusing on two potential treatment targets: the calcium and voltage-activated potassium ion channel (BK channel) and the cholinergic system.

CHANNEL TARGET
As the ion channel located on the presynaptic terminal of a neuron – that is, the axon terminal where different neurons make contact – the BK channel plays a role in regulating the excitability of cells and is highly unusual in that it is expressed in a number of different neuron transmitter systems rather than just one. It represents a new and exciting field of research. While some previous work has been done on the BK channel in frogs – with results suggesting that it provides the mechanism for fine-tuning synaptic strength – very little is known about how the BK channel mechanism functions in mammals. We know that the BK channel is expressed in many different...
neurons and that it influences synaptic strength – but the cellular molecular mechanisms in mammals have remained elusive until recently,” Schmid points out. “It is a relatively new target and there are currently very few drugs that we can use to block or enhance BK channel function in our experiments.”

Building on prior work that implies the BK channel fine-tunes the strength of the connection between two neurons, recent experiments conducted by Schmid and her team tested the short-term and long-term habituation of both reflexive and motivated behaviour in mice deficient for the pore-forming α-subunit of the BK channel. Interestingly, they found that the short-term habituation of reflexive behaviour was abolished in the BK knockout mice while the long-term habituation of both reflexive and motivated behaviour was unaffected by BK deficiency, thus indicating a clear distinction between the mechanisms for short-term and long-term habituation. Moreover, in another study the researchers found that mice with deficient BK channel function display impaired prepulse inhibition and spatial learning – and yet have normal working and spatial reference memory. Going forwards, an enhanced understanding of the role of the BK channel in sensory filtering will enable the development of specific drugs for improving sensory filtering and the symptoms associated with disruptions.

THE NICOTINE FACTOR

The network of nerve cells that uses acetylcholine in the transmission of nerve impulses – known as the cholinergic system – is the other key focus area in the Schmid Lab. In addition to its well-established role in higher cognitive functioning, there is strong evidence that acetylcholine is also involved in sensory filtering. Indeed, when nicotine enters the brain it attaches to acetylcholine receptors and mimics the neurotransmitter’s actions. A body of research has shown that schizophrenics who smoke show substantially improved prepulse inhibition and cognitive functioning than those who do not. Similarly, nicotine administered to healthy non-smokers has also been demonstrated to enhance prepulse inhibition. In this light, it is perhaps unsurprising that approximately 90 per cent of schizophrenia patients smoke and that their cognitive symptoms appear to improve by doing so.

Based on these insights, Schmid and her colleagues are determining the function of midbrain cholinergic cell groups in cognitive function and examining their interactions with non-cholinergic cells. To this end, they are combining cutting-edge optogenetic approaches in both in vivo and in vitro experiments with behavioural and electrophysiological approaches using their animal models of habituation and prepulse inhibition of startle. The hope is that this will enable them to assess the possibility of modulating the activity of the cholinergic system through pharmaceutical or electrical interventions.

TRANSLATION AND PROGRESSION

Ultimately, the basic and preclinical research conducted in the Schmid Lab is laying the foundation for the development of medication that enhances sensory filtering and cognitive function in humans. The identification of viable drug targets for the treatment of adverse cognitive symptoms will have a significant impact on the quality of life of patients with schizophrenia and autism, as well as on other groups who are affected by sensory filtering deficits. “Although we are still a very long way away from fully understanding these disorders and diseases, drugs that improve the cognitive function are extremely valuable,” Schmid asserts. “As developmental disorders, we may never be able to fully cure schizophrenia and autism – yet by treating the symptoms we can ensure that those afflicted will be able to live much more fulfilling and independent lives.”

Importantly, Schmid’s research could also have a wider impact on society at large: at present, health and welfare systems in Canada and elsewhere are burdened by a range of mental and neurodegenerative diseases that prevent individuals from operating at their full potential. The introduction of innovative new therapies for sensory filtering disorders represents a highly promising development for both individuals and the wider community. Until then, Schmid and her team will continue to apply their knowledge and expertise to probe the complex cellular mechanisms that are responsible for sensory filtering.