Exposing the mechanisms of sex-biased childhood developmental disorders

Noting that learning disabilities and developmental disorders are more prevalent in boys than girls, **Dr Jaclyn Schwarz** and her team at the Department of Psychological and Brain Sciences, University of Delaware are investigating the underlying causes. Looking at early-life immune activation and its interaction with intrinsic factors such as sex, they aim to improve our understanding of these problems and identify potential targets for therapeutic interventions.

Developmental disorders in children are relatively common, affecting nearly 14% of children in the United States of America. However, this broad term covers a range of disorders which affect normal childhood development. They may impact on one or several areas of development (including language, motor, social, and learning skills) and males are twice as likely to be affected as females. Learning disabilities, one of the most common forms of developmental disorder, are a case in point. Although these are often diagnosed early in childhood before the age of nine, when children are entering formal education, neuroscientists are only now uncovering how the brain matures during childhood to exhibit specific learning patterns at different ages. Researchers still know very little about how early life events can upset or modify this development; the observation that sex is clearly a factor has led Dr Schwarz and others to consider this a critical element in any investigations into the causes.

PROTECTOR TURNED PRODUCER

Dysregulation of the immune system is known to cause cognitive impairments in adults, including anxiety, depression and dementia; an emerging body of work now suggests that it also leads to behavioural and emotional disorders in children, but the precise mechanism is not clear. This is the focus of investigations in the Schwarz lab, with particular emphasis on how the sex of an individual is implicated. They hypothesise that neonatal infection results in significant developmental delays in learning and memory through its impact on the development of microglia (the cells responsible for immune defence in the central nervous system).

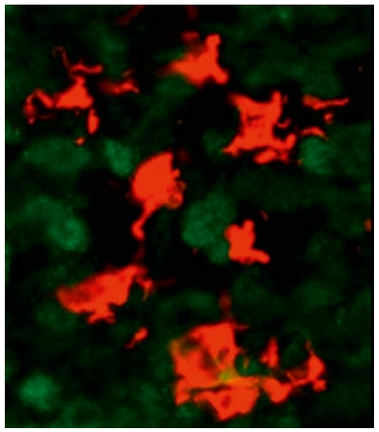
As very little is known about the developing immune systems of juveniles as opposed to adults, it is difficult to examine their impact on neuronal development. However, Dr Schwarz thinks that these subtle disturbances of neuronal development can result in significant changes in behaviour (such as those seen in children with developmental disorders).

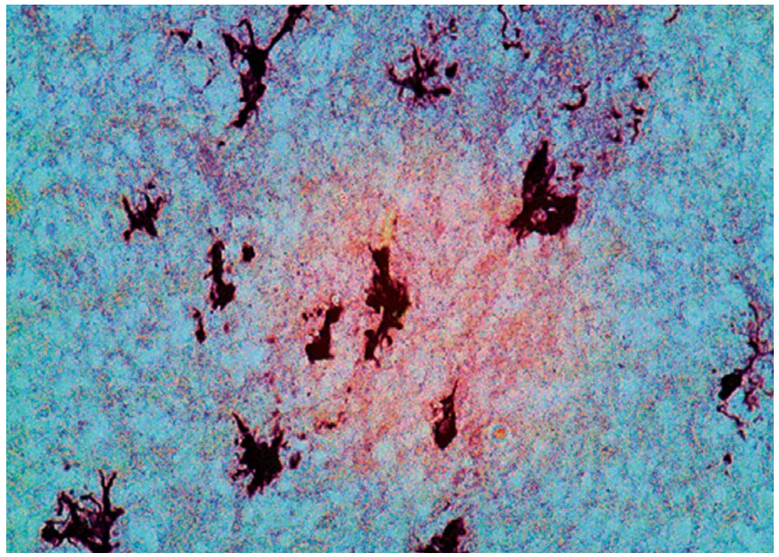
Using well-known measures of development and learning, such as spatial learning and memory associated with the hippocampus (a vital component of the brain associated with consolidating short-term memory to long-term memory), Dr Schwarz believes she will be able to test her hypotheses in rodent models with good translation to humans.

THE SHOCKING CONTEXT

The thrust of Dr Schwarz's research is based around a type of contextual fear conditioning. Rats are pre-exposed to a specific context (or not for controls) and allowed to explore freely. On later return to that context they immediately receive a small electric shock. Then, twenty-four hours later they are returned to the same context and their behaviour assessed for evidence of fear, showing they have been able to associate the shock with a specific context. Dr Schwarz's collaborators within the University of Delaware have shown that the ability to identify the context is related to

> **Through a series of experiments, Dr Schwarz aims to push forward understanding of the interactions between sex, immune activation and neuronal development**





Above and right: microglia in the developing brain

hippocampal development at a very early age.

Dr Schwarz and her team will take this a step further by exposing the neonatal rats to a low-grade infection, as well as using both male and female rats. Male neonates are known to produce a more robust response to infection than females, including significant increases in microglial volume and higher levels of cytokines (cell signalling molecules). For these reasons, Dr Schwarz expects to see a delay in contextual fear conditioning in infected males. It is already known that altered cytokine production in the hippocampus can significantly impact learning and memory, but these experiments will look at juveniles and crucially compare male and female responses.

GETTING UNDER THE SKIN

Coupled with these behavioural experiments will be an examination of the structure of microglia in the different groups and through the developmental process. A range of histological and molecular investigations will be performed to assess whether the morphology (shape) and number of microglia are affected, as well as investigating the presence of molecules known to promote plasticity in hippocampal development. This will assist the team in moving from the discovery of the underlying mechanisms affecting neuronal development (and therefore developmental disorders), to identifying targets for therapeutics which can rescue this process.

DEVELOPING A STRATEGY

In the search for potential therapeutic agents against these effects, the team propose minocycline as a promising candidate. This tetracycline antibiotic (a class of antibiotics which inhibit protein synthesis) is known to be lipid soluble and so able to cross the blood–brain barrier. Known to inhibit microglial-related processes associated with immune activation or infection, clinical trials have been undertaken on the basis that minocycline rescues synaptic abnormalities, inhibits neuroinflammation, and improves behaviours in rodent models. However, Dr Schwarz believes many issues remain unanswered. The rodent studies are often in adults, which the team have shown to have significantly different microglial morphology to juveniles. They also either use one sex exclusively or do not distinguish the data based on sex, another issue that the Schwarz lab have shown to be of prime importance in this field generally and minocycline therapies specifically.

> They hypothesise that neonatal infection results in significant developmental delays in learning and memory via its impact on the development of microglia

Through a series of experiments investigating physiological and behavioural responses to immune activation and minocycline treatment, Dr Schwarz aims to push forward understanding of the interactions between sex, immune activation and neuronal development. She is aiming to increase understanding to the point at which their findings can inform further study of clinical populations and result in drastically improved knowledge of sex differences in brain development.

Dr Schwarz is adamant that, 'it is necessary [to] determine the effect of minocycline on microglia and cognitive function in the juvenile brain of males and females'. By doing this in tandem with consideration of early life immune activation, their studies 'will help determine whether minocycline is an effective treatment for developmental disorders in both males and females'.

Q&A

What is the impact of early life developmental disorders on those affected?

The impact of developmental disorders is devastating because they are life-long and many of the disorders (e.g., autism, schizophrenia, or even learning disabilities) have no known causes let alone cures.

Why do you believe that such a range of outcomes may have such a simple common cause?

Immune activation can result from a number of different insults (triggers), but importantly, the end result of early-life immune activation may impact the brain, its development, and ultimately behaviour, dependent upon the timing of the initial insult or even subsequent insults that activate the immune system. This may hold the clue to the variability in outcomes that stem from simple immune activation, the result of possibly numerous insults to the developing foetus or infant.

How can you be confident that the animal models reflect the human conditions?

We can be confident that animal models reflect the human condition for a number of reasons. Primarily, the immune systems are relatively conserved across species. Similarly, the processes that underlie neural development are relatively conserved across species, though the timing of these processes may be different across species. Finally, animals (including rodents) are quite intelligent and capable of performing a number of learning tasks, they engage in social behaviours, and the neural structures that underlie these behavioural and cognitive processes are similar in humans and rodents.

What is the biggest challenge to the expansion of understanding in this field?

The biggest challenge towards understanding the causes of many neurodevelopmental disorders lies in our lack of understanding of what causes them. There is just so much that we do not understand about how the healthy "normal" brain works, let alone how neural function can be perturbed.

What led you to focus on this area?

I have always been fascinated by the developing brain and the plasticity it possesses. I also have a great passion for understanding how peripheral factors (hormones and immune function) can impact the brain. The brain does not function in isolation, but rather is influenced by the environment and one's physiology. I have also been very interested in sex differences in neural function, but especially how they may influence neurodevelopmental and neuropsychiatric disease. Until recently, females have been underrepresented in basic biomedical research and this has hindered our full understanding of the causes and possibly the cures for a number of important diseases and disorders of the nervous system. This has really compelled me to utilise both males and females in my own research given the strong sex-bias in so many neurodevelopmental disorders.

Detail

RESEARCH OBJECTIVES

Dr Schwarz's research focuses on the importance of sex factors in developmental disorders. Using rodent models, she is exploring how sex dictates the effect of neonatal immune activation on the brain and neural development.

FUNDING

National Institute of Mental Health

BIO

She received her BA in Psychology at Boston College in 2002. In 2008, she received her PhD in Neuroscience from the University of Maryland, School of Medicine. She was a postdoctoral fellow at Duke University from 2008-2012. She has been an Assistant Professor at the University of Delaware since 2013.

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