Exploring psychosis: how changes in white matter affect working memory

Dr Mariana Lazar is an Assistant Professor at the Department of Radiology at the New York University School of Medicine where she leads imaging research to examine anatomical and functional connectivity of the brain to gain a greater understanding of psychiatric and neurological diseases.

Psychotic spectrum disorders (PSD) currently affect roughly three percent of the population at an annual estimated cost of $62.7 billion in the US alone. Providing effective therapeutics is vital to speed up recovery. However, many of the causes and underlying neural mechanisms of PSD are still unknown, making it more difficult to advance treatment methods. Fortunately, Dr Mariana Lazar's work is currently shedding light on this area of research and aims to explore the underlying biological features of cognitive dysfunction.

Dr Lazar became interested in examining brain disorders during her post-doctoral research at the Waisman Laboratory for Brain and Behaviour at the University of Madison, Wisconsin. She received a PhD in Physics from the University of Utah and has been using her engineering and computational knowledge to apply a multidisciplinary approach to her research. Now an Assistant Professor at the Department of Radiology at the New York University School of Medicine, she employs magnetic resonance imaging, clinical and cognitive assessments, and genetic methods, to determine target areas for effective PSD treatments.

UNDERSTANDING THE HALLMARKS

Psychosis covers a wide spectrum of disorders with severe mental symptoms that include hallucinations, delusions and thought disturbances, paranoid beliefs, and unusual emotional manifestations. Schizophrenia often features as an umbrella diagnosis for PSD. Though cognitive dysfunction has long been thought of as a hallmark for more progressive stages in schizophrenia, studies found that cognitive impairment often pre-dates the illness and can act as a viable marker of PSD. Interestingly, working memory seems to be particularly compromised in PSD.

THE BRAIN'S RAM

Working memory represents the brain's ability to store, process and manipulate

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information to direct behaviour during ongoing tasks. By continuously updating and monitoring contents, it plays a vital role in higher-order cognitive processes including executive functions such as reasoning and learning. Located in the prefrontal cortex, primate studies have shown that lesions to this area of the brain can result in significant reduction in working memory function. However, working memory has a limited capacity, which means that humans can only retain a certain amount of information. This connection between working memory capacity and wider measures of cognitive ability is useful in examining the differences in PSD patients and healthy individuals. However, in order to understand cognitive deficits in PSD, it is necessary to uncover the biological basis of working memory capacity.

WHITE MATTER MATTERS

Dr Lazar's findings suggest that an impaired white matter microstructure in schizophrenia could be at the heart of deficits in working memory capacity. As such, the density of axons, myelination and surrounding cells such as glia may be directly impacted by psychiatric disorders. By applying the innovative approach of diffusion kurtosis imaging, which divides the magnetic resonance signal between intra- and extra-axonal white matter sections, Dr Lazar proposes that variability in visual working memory may be due to axon quality and density. Indeed, white matter tracts that are denser and more myelinated may preserve more information for processing. Similarly, larger axons can speed up processing and provide an essential link between nodes of the working memory network. In addition, Dr Lazar highlighted that extra-axonal structures may facilitate at least some of the visual working memory capacity.

MYELINATION DEFECTS REVEAL SHARED SYMPTOMS

Imaging studies have previously highlighted a reduction in white matter tracts in patients with schizophrenia. Similarly, post-mortem brain tissue examinations have supported such findings by demonstrating abnormalities in myelin in such patients. Localised to the prefrontal cortex as well as temporal and parietal regions, white matter degradation appears to be a consistent finding in schizophrenia. In addition, the demyelinating effects of metachromatic leukodystrophy (MLD) and multiple sclerosis may share some of the symptoms of PSD. Indeed, MLD is often accompanied by symptoms of psychosis, which can be

White matter pathways interconnect different brain regions and integrate brain activity
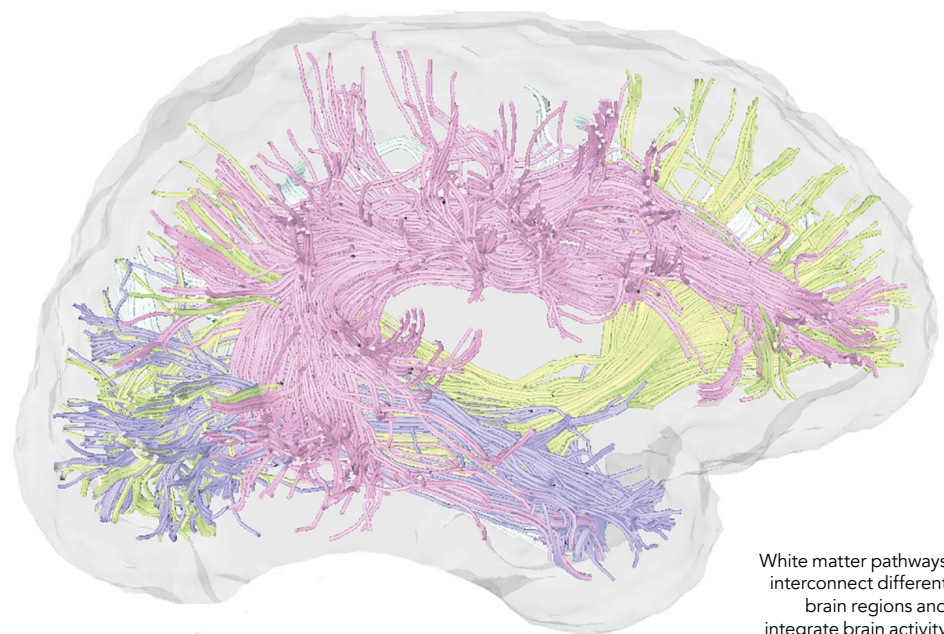
mistaken for schizophrenia. This suggests that demyelination and a loss of connectivity in prefrontal brain regions could be a shared feature in schizophrenia. Therefore, white matter should be further examined to determine its therapeutic potential in PSD.

White matter microstructural differences are not only associated with PSD, but also age-related neurological deficits and diseases including Alzheimer's disease. A loss of white matter volume of approximately 15% has been demonstrated among older participants. This has a direct effect on working and visual memory given white matter's effects on processing speed. Modifications to myelin structure may also result in slower information conduction.

LOSING THE CONNECTION

Current treatment approaches for PSD include antipsychotic medications, although pharmaceutical treatments often merely address the psychotic symptoms. Additionally, longitudinal research has found that certain antipsychotic medications may

boost a progressive decline in grey and white matter volume – signalling a negative effect on working memory.

A potentially more successful intervention to directly target working memory is through cognitive training. Though still poorly understood, cognitive therapy may enhance attention processing and working memory function by influencing underlying cortical connectivity. Research suggests that neuroplasticity may best be enhanced through a combinatorial strategy, which involves cognitive training as well as medical approaches.

Ultimately, this reconnection of connectivity between neural substrates proves an area worth further investigation in PSD. By helping to decipher the biological basis of working memory processes, Dr Lazar's research has the potential to address the critical limitations within this field.

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Q&A

Your background is very diverse. How did you become interested in studying psychotic disorders?
I became interested in medical physics when I started my PhD at University of Utah in Salt Lake City since it combined my interest in computational science, physics, and biological modelling. My PhD thesis focused on developing non-invasive imaging methods to map white matter pathways connecting different brain regions. Schizophrenia has long been considered a disorder of connectivity. Thus, I believed that the techniques I developed could make a true impact in understanding the biology of the disease. Once I started to learn about the field I became deeply motivated to build a research programme that will ultimately contribute to a better life for people affected by these disorders. I believe that my multidisciplinary background offers a broader perspective and a more synergistic approach in overcoming the challenges related to understanding the complex and multifaceted psychiatric disorders.

Could you share some of the novel therapeutic strategies currently in the making which you believe may have a positive impact on schizophrenia therapeutics in the future?
A critical limitation of current treatments is their inability to address cognitive dysfunction. This has a strong impact on the day to day life of people with schizophrenia – it affects their ability to finish their education, maintain a job, and lead productive lives. A primary reason for the lack of treatments is the lack of understanding of what motivates cognitive dysfunction at the biological level. Our work aims to address this limitation by testing several mechanisms that may link white matter deficits to cognitive dysfunction. If our hypotheses are confirmed they will ultimately lead to novel treatments to improve cognitive function.

How could genetic approaches be used to examine myelination in PSD?
We hypothesise that people born with deficits in certain white matter-related genes are more likely to end up with myelination-deficient axonal pathways. However, this link

has yet to be established. Moreover, it's not yet known which of the genetic mutations observed by the large-scale genetic studies are the ones ultimately affecting myelin or white matter more generally. By combining genetic and imaging assays we aim to start addressing these questions and define biomarkers that may be used to identify people at risk for developing myelin deficits and cognitive impairment.

What are the challenges associated with examining white matter density and decline in the brain?
MRI techniques offer the unique opportunity to examine white matter structure and organisation non-invasively and in vivo. However, they have limited resolution, with the measuring unit, called voxel, on the order of one–two mm. In contrast, white matter microstructural constituents have micron-scale sizes. Thus, our signal is an average of signals coming from many structures. Current approaches aim to develop models of the MRI signals coming from different sources and thus describe, indirectly, different microstructural features (i.e., axonal versus extra-axonal spaces). Novel data suggest that these approaches are able to give good estimates of mean axonal density in a voxel.

The latest research you've participated in uses 3D Multivoxel MR Spectroscopic Imaging. What are the opportunities and drawbacks of this technology?
MR spectroscopic imaging estimates the concentration of several metabolites that have important roles in brain functioning. These metabolites reflect different aspects of brain function such as density of viable neuronal tissue, membrane metabolism, or glial function. Spectroscopy can thus tell us the integrity of these processes in the brain. MR spectroscopy drawbacks are primarily related to the long imaging times and relatively coarse resolution, with current achievable voxel sizes of the order of several millimetres. Computational approaches are currently used to tease apart signals obtained from different tissues and structures and thus compensate for the large voxel sizes.

Detail

RESEARCH OBJECTIVES
Dr Lazar's research fundamentally focuses on understanding the roots of brain disorders. Her latest research looks at Psychotic Spectrum Disorders (PSD), where she hopes to determine target areas for effective treatments.

FUNDING
The National Institute of Mental Health (NIMH)

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BIO
Dr Lazar studied a BS and an MS in Physics at the University of Bucharest. She later went on to obtain another MS in Computational Science and Engineering and a PhD in Physics at The University of Utah. She currently works as an Assistant Professor at New York University.

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