Alzheimer's-related (amyloid, tau), and inflammatory markers (eg, soluble triggering receptor expressed on myeloid cells 2, and different cytokines) in the CSF. No change was found in cognitive function over time, but individuals with chronic pain and suspected non-Alzheimer disease pathophysiology developed increased T-tau and souble TREM2 CSF levels over time. This finding indicates that chronic pain is associated with neuronal damage and brain inflammation and might influence neurodegeneration.

Progress has been made in understanding chronic pain, and the new findings need to be used to implement better strategies for chronic pain prevention and treatment. A randomised controlled trial by Jones and colleagues showed a positive effect of a selective sodium channel inhibitor, a class of drugs that has been studied with mixed results for the past 10 years.[8,9] The new study examined the efficacy of VX-548, a selective NaV1.8 inhibitor, in managing acute postoperative pain after abdominoplasty or bunionectomy (577 participants in total).[9] The study had four treatment arms and compared two different doses of VX-548 with a common pain medication (hydrocodone bitartrate and acetaminophen) or placebo over 48 h. Effectiveness, assessed as the sum of the pain intensity difference over 48 h, was significantly better in the group treated with high-dose VX-548 compared with placebo irrespective of whether people had abdominoplasty or bunionectomy, and side-effects were tolerable. Although chronic pain was not assessed in this trial, effectively reducing acute postoperative pain with few side-effects could be an important step toward prevention of chronic pain.

In summary, studies from the past year have supported the concepts that acute localised pain can spread to other regions and become chronic; that feelings of despondency, tiredness, and stress are risk factors for the development of chronic pain; and that pain has potential neurogenerative consequences. Treating localised (eg, postoperative) pain early and effectively might in the future be one way to reduce the prevalence of chronic pain.

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Neuropsychiatric research in 2023: mechanisms of stress and therapies

Psychiatric disorders are a leading cause of disability and suicide worldwide.[1] Understanding their underlying molecular and cellular mechanisms is crucial for the development of new, fast-acting, and efficacious treatments. In this Round-up, we highlight five key research studies that advanced our understanding of the mechanisms of stress-induced and stress-linked psychiatric disorders and their treatments in 2023.

Social status and personality traits can offer considerable insight into the neurobiological basis of stress regulation and can have a substantial impact on health and wellbeing.[2] By forcing dominant mice to lose a dominance test against their subordinates,

Zhengxiao Fan and colleagues[3] identified a molecular mechanism in the lateral habenula that promotes depressive-like behaviours. Using in-vivo fibre photometry and single-unit electrophysiological recordings, the authors showed that the forced loss of social status, as opposed to natural loss, generates a negative reward prediction error, which activates the brain's anti-reward centre in the lateral habenula and inhibits signals in the medial prefrontal cortex, which controls social competitiveness. In this study, depressive-like behaviours were mitigated by the use of the antidepressant ketamine or via optogenetic activation of the medial prefrontal cortex. The identification of this neural circuit provides a mechanistic foundation for interventions to treat mood disorders caused by social-psychological factors.

Severe exposure to stressful stimuli can worsen inflammatory responses, as it is the case in inflammatory bowel disease.[4] Kai Marcus Schneider and colleagues[5] identified a mechanism that explains how psychological stressors can exacerbate inflammatory bowel disease in an animal model. Using complementary strategies, the authors found that chronic exposure to glucocorticoids after psychological stressors can promote the generation of inflammatory glial cells. The authors also showed how glucocorticoids can impair the muscles of the digestive system. Importantly, their findings were validated in three independent cohorts of patients with inflammatory bowel disease. These findings not only provide a new mechanism for the impact of prolonged stress exposure, but also define the enteric nervous system as a mediator for psychological stress and inflammation in the gut. Ultimately, these findings highlight the relevance of considering the psychological status of patients during treatment for inflammatory bowel disease.

Another system that interacts with the brain and is involved in the response to stressful challenges and subsequent feelings of anxiety is the cardiovascular system. Karl Deisseroth and his research team[6] bioengineered a non-invasive tool to optogenetically manipulate cell-type-specific cardiac rhythms in mice, by using wearable vests emitting red light. They showed that artificially increasing the heart rate of mice enhanced anxiety-like behaviours. Using advanced electrophysiology and whole-brain activity recordings in freely moving mice, they found that the posterior insular cortex was activated when the heart rate increased during an anxiety-provoking situation. These findings suggest that this brain region is a key relay centre for peripheral signals coming from the heart after exposure to a potential threat. This brain–heart pathway might have important implications for the development of new therapeutic approaches for the treatment of anxiety and other stress-related disorders.

Adolescence is a crucial developmental period during which psychiatric symptoms can emerge.[7] An international effort led by researchers in China, Germany, and the UK used several large population-based neuroimaging cohorts consisting of thousands of adolescents to identify a shared neural basis for psychiatric disorders.[8] The authors investigated how environmental, psychological, and biological factors during adolescence might influence psychological outcomes. Adolescents with different mental health disorders had similar patterns of activity in the frontal lobe of their brains. The authors substantiated their findings using data from thousands of additional adolescents and identified an association with a genetic variant that had been previously associated with synaptic

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pruning and stress-related disorders. These findings suggest that the disruption of synaptic pruning can affect how different brain regions communicate with each other and help in the development of new therapeutic interventions.

Lack of response to antidepressants is a major issue for people with depression and other stress-related disorders.[9] However, the discovery that a single administration of a selected group of new treatments, such as ketamine or psychedelic compounds, can produce a rapid and long-lasting antidepressant response has led to a rethinking of how antidepressants work in the brain. A study conducted by David E Olson and colleagues[10] described how the activation of intracellular 5-hydroxytryptamine (serotonin) 2A receptors (5-HT2ARs) is necessary for the antidepressant properties of psychedelic compounds. Using a combination of genetic and molecular tools, the authors showed that intracellular 5-HT2ARs mediate the plasticity-promoting properties of these compounds. These findings highlight a location bias (intracellular *vs* extracellular) in how these drugs interact with serotonin and serotonin receptors within cells. This study might lead to the development of specialised treatment interventions for people with neuropsychiatric disorders.

Overall, 2023 was an exciting year for new developments in neuropsychiatry. Nevertheless, much more research and progress are needed for the development and implementation of faster and more efficacious treatments of stress-induced psychiatric disorders.

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Neurological infections in 2023: surveillance and prevention

Neurological infections remain a public health challenge worldwide. A comprehensive analysis from the Global Burden of Disease Study 2019 revealed that substantial progress has been made in reducing mortality and morbidity associated with meningitis over the past three decades,[1] but there is still much work to be done. In 2023, advances have taken place in four key areas of neurological infection research: immunisation, surveillance, health services, and treatment.

Primary prevention remains crucial in the battle against neurological infections, especially in regions with a high prevalence of bacterial meningitis. These regions face an urgent need for effective and affordable vaccines. In response to this challenge, the Serum Institute of India, in collaboration with the global health organisation PATH, developed an economical pentavalent meningococcal ACWYX conjugate vaccine, known as NmCV-5.[2] To assess the performance of this vaccine, a randomised controlled trial was done, involving 1800 participants aged between 2 and 29 years in Mali and Gambia.[2] The primary outcome of this trial was the immunogenicity of NmCV-5 compared with that of the licensed quadrivalent meningococcal conjugate vaccine MenACWY-D. Results showed that the immunogenicity of NmCV-5 was non-inferior to that of MenACWY-D, generating a robust response to all four serotypes in common with the MenACWY-D vaccines, as well as against serogroup X. These findings hold great promise for enhancing control of epidemic meningitis in Africa.

Enhanced surveillance systems, including bacterial whole-genome sequencing, are imperative for

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