PROGRESS IN MIND | Psychiatry & Neurology Resource Center

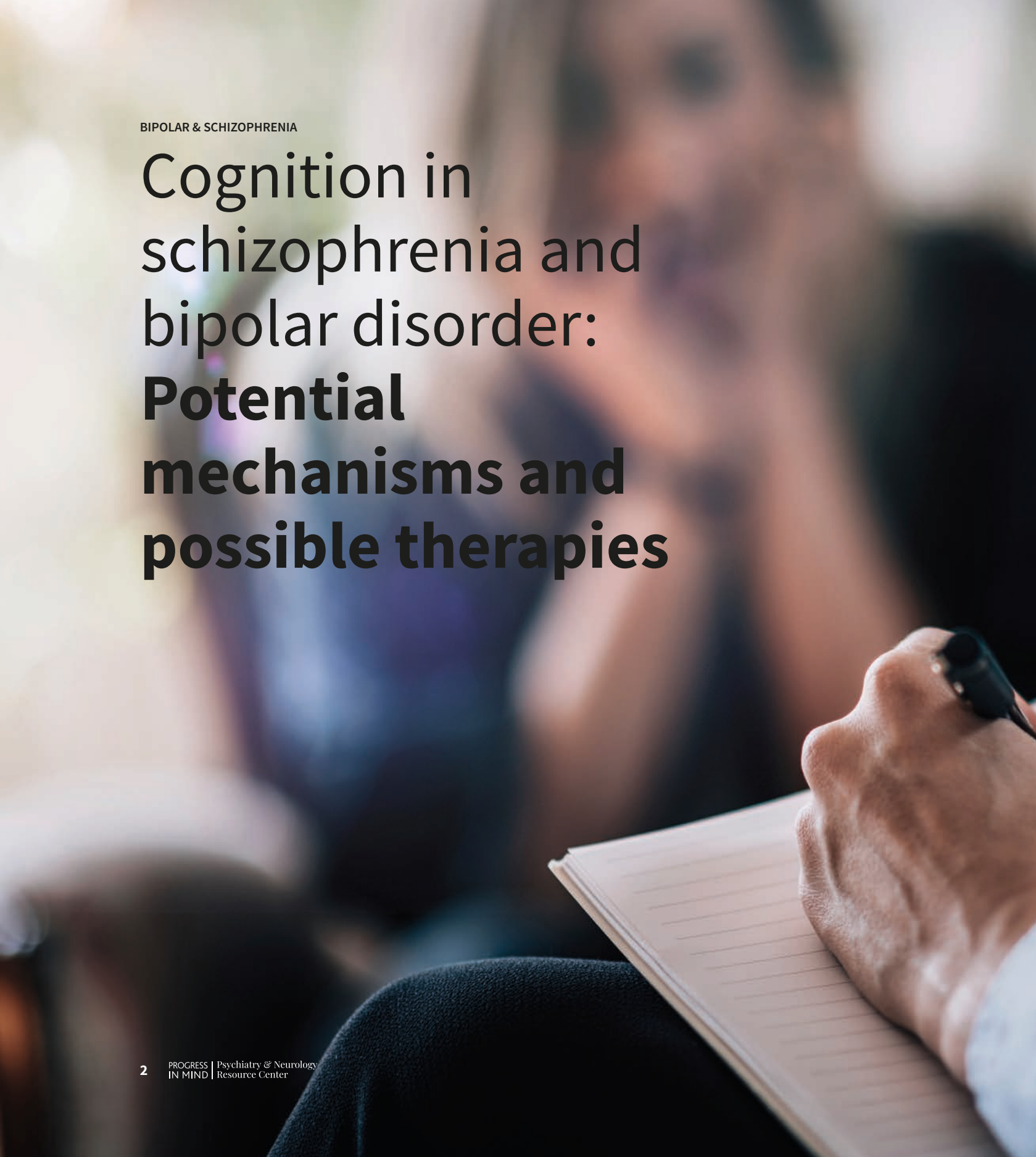
Psychiatry & neurology knowledge that matters to you

ECNP 2023 *Barcelona*

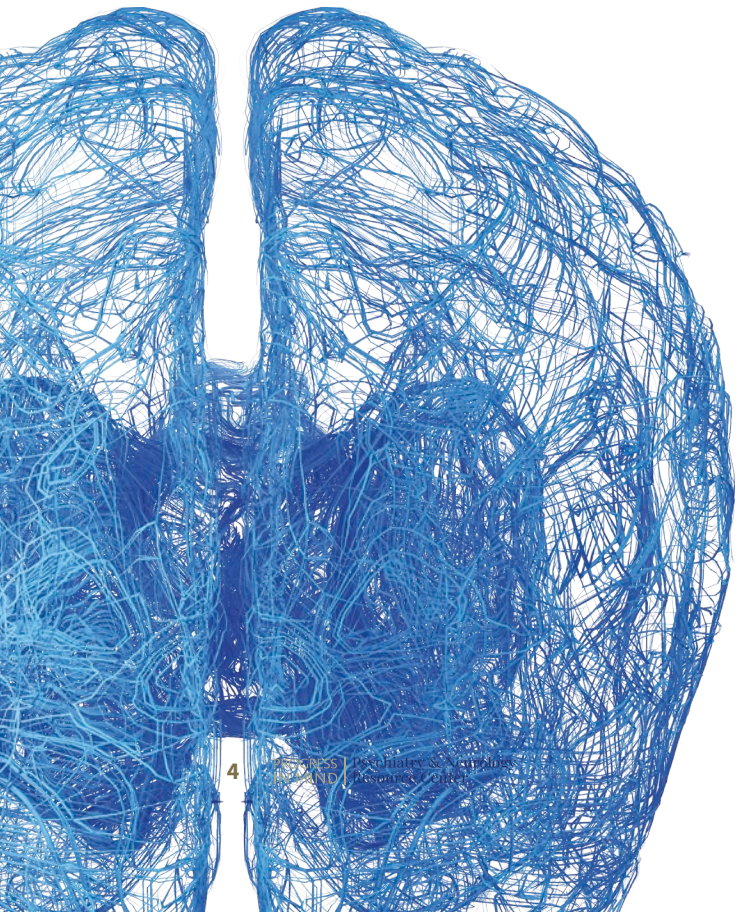
7-10 October

Lundbeck

Cognition in schizophrenia and bipolar disorder: **Potential mechanisms and possible therapies**



At the 35th ECNP Congress in Vienna, Austria (15th–18th Oct), Dr Ingrid Melle (University of Oslo, Oslo University Hospital, Oslo, Norway) first discussed how cognitive problems can be a key feature of schizophrenia and bipolar disorder. Such problems have been linked to 'overpruning' of synaptic densities and to changes in thalamic activity during sleep, associated with memory consolidation. Cognitive difficulties can affect both functioning and social cognition in patients with schizophrenia or bipolar disorder. Dr Rebecca Strawbridge (institute of Psychiatry, Psychology & Neuroscience, London, UK) then discussed cognitive remediation therapy, which has been shown over the past few decades to help people develop cognitive skills that can be utilised in their everyday lives.



Cognition in schizophrenia and bipolar disorder

Cognitive problems develop early in patients with schizophrenia and bipolar disorder and may remain an issue throughout life.[1,2] In cell culture models of schizophrenia, inflammation-mediated 'overpruning' leads to synaptic density reduction in fibroblasts compared to healthy controls.[3] This may be, postulated Dr Melle, related to the cognitive deficits seen in schizophrenia.

Sleep is another factor that can affect cognition. Sleep is needed for memory consolidation,[4] which involves 'sleep spindles' seen on EEG reflecting small bursts of activity in the thalamus during, predominantly, non-REM sleep.[5] In patients with schizophrenia and bipolar disorder, sleep spindle density is decreased.[6,7]

> *Cognitive difficulties can impact functionality and social cognition*

It is well established that cognition is linked to functional outcomes in patients with schizophrenia.[8] As such, in the 11th revision of the International Classification of Diseases, cognitive symptoms are now included in the diagnostic description of schziophrenia.[9] Cognitive deficits can not only directly impact quality of life and functioning, but also indirectly, through their effects on social cognition.[10] These include domains, such as empathic accuracy, managing emotion, self-referential memory, the ability to detect lies or sarcasm and facial affect recognition.[2]

Improving cognition in schizophrenia and bipolar disorder

It is important to address cognitive functioning in schizophrenia and bipolar disorder to help patients gain and maintain recovery.[11] Accordingly, cognitive interventions for schizophrenia and bipolar disorder have been proposed.[12,13] Cognitive remediation therapy (CRT) encompasses a number of psychological/behavioural interventions aimed at cognitive rehabilitation and improving functionality.[14] CRT for schizophrenia has been developed over the past 50 years. Meta-analyses showed significant cognitive gains produced by CRT, along with some effects on functioning and symptoms.[15]

CIRCuiTS is a type of CRT that teaches strategies and promotes metacognitive knowledge and regulation to help a patient understand and regulate their cognitive faculties. This therapy is validated in patients with schizophrenia for its ability to improve cognitive and functional outcomes. CIRCuiTS is delivered remotely in a 1:1 manner along with homework sessions. It includes goal setting and involves tasks that can be applied to real-life situations. For instance, cognitive tasks that can be abstract then can be practised online in a virtual village.[16,17] While results of a large, multicentre study of CIRCuiTS is ongoing, the practical aspects of the trial have been published.[18]

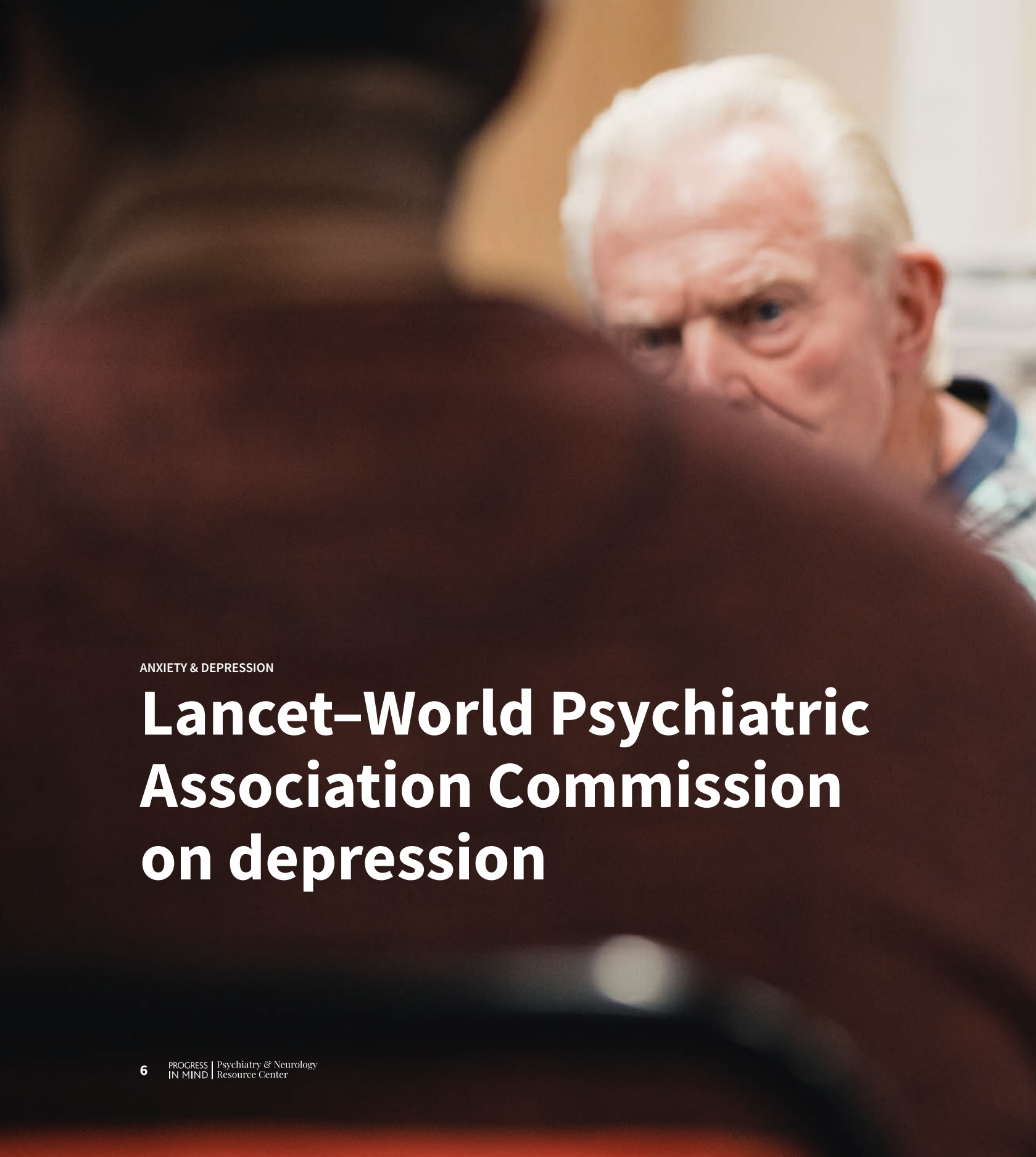
> *Cognitive remediation therapy can help build cognitive faculties*

CRT for bipolar disorder has a shorter history, with studies from 2010 onwards showing benefits on areas, such as problem solving and working memory.[19] These include programs that extend over a number of weeks or months and include, or are only, computer-based elements.[20-22]

For bipolar disorder, Dr Strawbridge highlighted how large, high quality, randomised controlled trials are needed. Methodology papers are available to inform current practice. These recommend that CRT programs for patients with bipolar disorder target those with objectively measured cognitive impairments.[22,23] CRT has also been combined with functional remediation with positive outcomes.[24,25]

There are few studies that investigate pharmacological therapies for cognitive difficulties in patients with schizophrenia or bipolar disorder. However, while some improvements in cognitive variables have been shown with a diverse array of agents, more studies are needed.[26-28] The International Society for Bipolar Disorders Targeting Cognition Task Force also suggest other non-pharmacological options to address cognitive features of bipolar disorder including repetitive transcranial magnetic stimulation and transcranial direct current stimulation.[22,29,30]

1. Lewandowski KE, et al. Psychol Med. 2011; 41: 225-241.
2. Lee J, , et al. Am J Psychiatry. 2013; 170: 334-341.
3. Sekar A, , et al. Nature. 2016; 530: 177-183.
4. Walker MP, et al. Neuron. 2002; 35: 205-211.
5. Klinzing JG, et al Nat Neurosci. 2019; 22: 1598-1610.
6. Ferrarelli F, et al. Am J Psychiatry. 2007; 164: 483-492.
7. Ritter PS, et al. Acta Psychiatr Scand. 2018; 138: 163-172.
8. Green MF. Am J Psychiatry. 1996; 153: 321-330.
9. World Health Organization. ICD-11 for Mortality and Morbidity Statistics (Version : 02/2022). 6A20 Schizophrenia. 6A25.5 Cognitive symptoms in primary psychotic disorders. bit.ly/3T0w6KD. Published 2022. Accessed: 07 Nov 2022.
10. Fett AK, et al. Neurosci Biobehav Rev. 2011; 35: 573-588.
11. Tsapekos D, et al. Bipolar Disord. 2020; 22: 213-215.
12. Green MF. Am J Psychiatry. 1993; 150: 178-187.
13. Goldberg JF, Chengappa KN. Bipolar Disord. 2009; 11 Suppl 2: 123-137.
14. Wykes T, et al. Br J Psychiatry. 2007; 190: 421-427.
15. Lejeune JA, et al. Schizophr Bull. 2021; 47: 997-1006.
16. Reeder C, et al. Behav Cogn Psychother. 2016; 44: 288-305.
17. Cella M, et al. Front Psychol. 2015 ;6: 1259.
18. Wykes T, et al. Trials. 2018; 19: 183.
19. Deckersbach T, et al. CNS Neurosci Ther. 2010; 16: 298-307.
20. Strawbridge R, et al. Bipolar Disord. 2021; 23: 196-208.
21. Ott CV, et al. Bipolar Disord. 2021; 23: 487-499.
22. Miskowiak KW, et al. Bipolar Disord. 2022; 24: 354-374.
23. Miskowiak KW, et al. Eur Neuropsychopharmacol. 2016; 26: 1541-1561.
24. Gomes BC, et al. Bipolar Disord. 2019; 21: 621-633.
25. Torrent C, et al. Am J Psychiatry. 2013; 170: 852-859.
26. Hsu WY, et al. Front Psychiatry. 2018; 9: 91.
27. Miskowiak KW, et al. J Clin Psychiatry. 2014; 75: 1347-1355.
28. Burdick KE, et al. Neuropsychopharmacology. 2020; 45: 1743-1749.
29. Myczkowski ML, et al. J Affect Disord. 2018; 235: 20-26.
30. Bersani FS, et al. J Affect Disord. 2017; 209: 262-269.



ANXIETY & DEPRESSION

Lancet–World Psychiatric Association Commission on depression

A joint Lancet and World Psychiatric Association Commission on depression calls for a united action between healthcare practitioners, policy makers, researchers, and the general community including people with lived experience of depression to lower the global burden of depression. Three experts who played lead roles in the Commission presented an overview of the key messages and recommendations at World Congress of Psychiatry 2022.

A neglected global health crisis

The burden of disability due to depression is highest in young adults in their second and third decades of life and in low and middle-income countries,[1] said Professor Helen Herrman, Centre for Youth Mental Health, University of Melbourne, Australia. This burden affecting young adults leads to impaired work performance, income, and personal relationships.[1]

> *The burden of disability due to depression is highest in young adults and in low and middle-income countries*

Yet, the burden of depression in terms of age-adjusted disability life years/100,000 population has remained unchanged over the past 30 years.[1] This contrasts with the appreciable reduction in the global burden of cardiovascular disease over the same time.[1]

> *In high- and low-income countries only 14% and 6% of patients, respectively, receive adequate pharmacotherapy, and 17% and 8% of patients, respectively, receive adequate psychotherapy*

Only 52% of patients in high-income countries and 27% in low-income countries have any contact with services, only 14% and 6%, respectively, receive adequate pharmacotherapy, only 17% and 8%, respectively, receive adequate psychotherapy.[1]

Interventions are needed at multiple levels to reduce the global burden of depression, said Professor Herrman. These need to address public understanding and political will, to drive prevention at societal and individual levels, and to enable access to effective care.[1]

Key messages on diagnosis and management

Depression is a common, heterogeneous condition associated with a clinically recognizable set of symptoms that cause distress and interfere with normal function in everyday life,[1] said Professor Mario Maj, Department of Psychiatry, University of Campania L Vanvitelli, Naples, Italy. It occurs worldwide with the most prevalent symptoms varying from region to region, reflecting culture and context.[2]

> *Each patient needs a personalized management plan that addresses their unique combination of symptoms and experience*

Every individual with depression has their own unique personal combination of symptoms and experience, so each patient needs a personalized management plan.[3] This plan also needs to take into account the clinical stage of the depression, whether it is at an early intervention stage or recurrent and persistent,[1] explained Professor Maj.

> *Whole-of-society engagement is needed to translate current knowledge into practice and policy*

Collaborative care delivery models involving the primary care team, the mental health specialist team, families, lay counsellors and cross-sector providers are advocated by the commission,[1] said Professor Maj. In addition, the commission advocates for increased investment with whole-of-society engagement involving families, schools, workplaces, neighborhoods, and health services, to translate current knowledge into practice and policy and to upgrade the science agenda.[1]

> *Prevention and investment strategies are needed to address inequities*

Recommendations for action by four primary stakeholders

Professor Vikram Patel, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, provided an overview of the commission's recommendations for action to reduce the burden of depression by the four primary stakeholders as follows:[1]

- For healthcare practitioners, especially these in primary care — To increase their understanding of the diverse heterogeneous presentations of depression, manage the whole person (not the diagnosis), and to provide personalized care using a collaborative care model
- For policy makers — To respond to the evidence and implement prevention and investment strategies to address inequities across the life course, especially for those in the second and third decades of life
- Most people with depression will recover with the right support and treatment
- For researchers — To further investigate the multifactorial causation of depression and who will respond to which treatment to provide evidence for precision medicine management
- For the general community and people with the lived experience of depression — To recognize the importance of seeking help early to increase the chance of recovery and to remain hopeful, because most people with depression will recover with the right support and treatment

1. Herrman H, Patel V, Kieling C, et al. Time for united action on depression: a Lancet-World Psychiatric Association Commission. Lancet. 2022;399(10328):957–1022.
2. Haroz EE, Ritchey M, Bass JK. How is depression experienced around the world? A systematic review of qualitative literature. Soc Sci Med. 2017;183:151–62.
3. Maj M, Stein DJ, Parker G, et al. The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry. 2020;19(3):269–93.

The role of sleep disorders in depression and anxiety

In the symposium 'Assessment and management of sleep disorders in anxious and depressed patients,' presented at the 35th ECNP Congress in Vienna, Austria (15th–18th Oct), Prof Francesco Benedetti (University Vita-Salute San Raffaele, Milan, Italy) discussed how light can directly impact not only the circadian rhythm, but neurological systems involved in mood and sleep as well as immune system factors. This is reflected by the rise of seasonal affective disorder in winter months. Light therapy, which can be combined with sleep deprivation therapy, can lead to rapid and lasting antidepressant effects. Dr Laura Palagini (University of Ferrara, Italy) described how hyperarousal shown in people with insomnia is similar to that in people with anxiety disorders. Accordingly, both conditions can drive each other and may need to be evaluated and treated together. Such treatments include cognitive behaviour therapy.

Links between the circadian rhythm, sleep disorders and depression

Light can directly influence neurotransmitter release. For instance, when days are short, in rats, there is increased dopamine signalling in the hypothalamus, which decreases somatostatin neuron function, resulting in decreased corticotropin-releasing factor (CRF) and lower CRF and corticosteroid plasma levels. This is associated with decreased stress behaviour due to a preference for nocturnal living in rats. In light-preferring humans, the opposite occurs during shorter days and there are increased stress behaviours and depression.[1]

If the circadian system is disrupted, the immune system response, hypothalamic-pituitary axis and metabolic rhythms can also be disrupted and mood may be affected.[2] Correspondingly, severity of myriad diseases, including metabolic disorders and neurological and psychiatric conditions, can be affected by circadian disruption.[3] There is evidence of genetic vulnerabilities in circadian rhythm associated genes in people with mood disorders leading to a misalignment of circadian rhythms and homeostatic regulators.[4] Additionally, early life, including pre-natal stress, can result in sleep difficulties and altered circadian regulation that may impact epigenetically to produce a later vulnerability to mood disorders.[5]

> *Circadian rhythm disruptions can be found in, and drive, mood disorders including depression and bipolar disorder*

Usually sleep is regulated by a circadian process and driven by 'sleep debt' whereby a person becomes sleepier the longer they stay awake. In mood disorders, there is less build-up of sleepiness and circadian rhythm shifts and disruption.[6] Sleep disorders are particularly seen in people with depression and portend depressive episodes.[7] Changes include sleep cycle alterations, fragmented sleep, fewer rapid eye movement (REM) sleep episodes and early morning awakening.[8]

In healthy people, the mid-point of sleep should occur 6 hours after dim light melatonin onset. Seasonal affective disorder (SAD) scores increase in people where this mid-point is higher or lower than normal.[9] There are also increases in the level and amount of time melatonin is released.[10] Similarly, in a study of adolescents and young people with mood disorders, those with depression showed significantly higher levels and sooner onset of melatonin secretion compared to patients with bipolar disorder. Both showed a flattening of the melatonin peak.[11]

Additionally correlated with SAD symptom severity are seasonal increases in serotonin transporter levels (leading to less available serotonin).[12] C-reactive protein and neutrophils, markers of inflammation, also rise in winter months, and there is a decrease in lymphocyte levels.[13] This is important in sleep biology as cytokines contribute to sleep timing.[14] In people with SAD, there is a significant increase in interleukin-1 and tumour necrosis factor-a concentration and macrophage activity and decrease in lymphocyte proliferation.[15]

> *Combined light therapy and sleep deprivation can have rapid antidepressant effects*

Light therapy has been trialled for treating mood disorders with efficacy either alone[16] or in conjunction with antidepressants shown.[17] Such therapy can increase serotonin activity, enhance dopamine release, increase levels of noradrenalin and desensitise glutamate n-methyl-D-aspartate (NMDA) receptors.[18] Light therapy effects are best, said Prof Benedetti, when it is administered in the morning, 8 hours after the melatonin peak the day before.[19] Estimates of melatonin peak times can be ascertained using the Morningness-Eveningness Questionnaire.[20] In people with SAD undergoing light therapy, the above-discussed increases in inflammatory factors, and changes in immune system cells, can be reversed.[15]

While full sleep or partial sleep deprivation in the first part of the night can drive depression, total sleep deprivation or deprivation in the second part of the night can have antidepressant effects.[21] Sleep deprivation has also been shown to restore synaptic plasticity deficits[22] and rebuild white matter microstructure connectivity.[23] Combining light and sleep deprivation therapy, Prof Benedetti discussed a protocol whereby patients receiving lithium remain awake for three sets of 36 hour periods over a week, with light therapy in the morning on days where night-time sleep is allowed. This leads to an immediate drop in depression scores that continues throughout the week. In a study of this regimen, there was a 70% response rate and while 21% of these patients relapsed, overall remission was shown in 55% of patients.[24]

Links between insomnia and anxiety

Insomnia can be a stress-related disorder with contributing psychological and biological factors.[25] It can both drive and be driven by emotional and cognitive arousal, leading to dysfunctional cognitions (such as rumination and worry), maladaptive habits (such as daytime napping and an irregular sleep schedule) and consequences of these factors, including fatigue, social discomfort, mood disturbances and performance impairments. These domains also interact with and trigger each other to exacerbate insomnia even more.[26]

Insomnia is also associated with accumulation of waste products in the brain that are usually disposed of during sleep, increased neuroinflammation and a reduction in connectivity between the amygdala and medial prefrontal cortex (PFC), brain areas associated with stress and emotional regulation.[27] There is also reduced activation of the PFC and head of caudate, accompanied by overactivation of the arousal system.[28] Another finding in people with insomnia is problems with REM sleep similar to that seen in depression. Here, emotion processing is disrupted with corresponding continued amygdala activation.[29]

Hyperarousal in insomnia may interact with hyperarousal in anxiety disorders

In anxiety disorders, there is also hyperactivation of the brain's stress system, involving the medial PFC, hippocampus and amygdala[30] as well as inflammatory activation.[31] As insomnia may have a role in anxiety disorders, it's important, said Dr Palagini, to assess the potential clinical and neurobiological links between the two. One meta-analysis showed that insomnia conveys a 2–3 fold risk for development of an anxiety disorders.[32] Insomnia is itself exacerbated by aspects of anxiety such as worry, perceived stress, negative thinking and rumination and may in turn fuel these factors.[33] Clinically, insomnia may also drive hypervigilance and cognitive overstimulation, again leading to development and exacerbation of anxiety disorders.[34] In a study carried out by Dr Palagini, she found a link between low resilience, emotional dysregulation and pre-sleep cognitive hyperarousal.[5] There is also evidence that the neuroinflammation linked to insomnia may add to anxiety-related factors such as brain plasticity.[34]
These findings are not surprising as there is overlap in the brain of regions involved in both anxiety and insomnia, such as the PFC, anterior cingulate cortex and amygdala.[35,36]

Cognitive behaviour therapy can help improve insomnia and anxiety disorders

Orexin neurons, located in the lateral hypothalamus, are responsible for the 'flip' from wakefulness to sleepiness and 'flop' back. They normally receive excitatory inputs and project to ventral tegmental area dopaminergic neurons and locus coeruleus noradrenergic neurons. This can be increased during times of stress and anxiety.
Thus, proposed Dr Palagini, there may be a role for orexin in insomnia.[37]

1. Dulcis D, et al. Science. 2013; 340: 449-453.
2. McClung CA. Biol Psychiatry. 2013; 74: 242-249.
3. Sulli G, et al. Trends Pharmacol Sci. 2018; 39: 812-827.
4. Benedetti F, et al. Biol Psychiatry. 2013; 74: 236-237.
5. Palagini L, et al. J Affect Disord. 2019; 243: 121-132.
6. Borbély, et al. J Sleep Res. 2016; 25: 131-143.
7. Bauer M, et al. Bipolar Disord. 2006; 8: 160-167.
8. Nutt D, et al. Dialogues Clin Neurosci. 2008; 10: 329-336.
9. Lewy AJ, et al. Proc Natl Acad Sci U S A. 2006; 103: 7414-7419.
10. Wehr TA, et al. Arch Gen Psychiatry. 2001; 58: 1108-1114.
11. Robillard R, et al. Eur Psychiatry. 2013; 28: 412-416.
12. Mc Mahon B, et al. Brain. 2016; 139: 1605-1614.
13. Wyse C, et al. iScience. 2021; 24: 102255.
14. Imeri L, Opp MR. Nat Rev Neurosci. 2009; 10: 199-210.
15. Song C, et al. J Affect Disord. 2015; 185: 90-96.
16. Golden RN, et al. Am J Psychiatry. 2005; 162: 656-662.
17. Lam RW, et al. JAMA Psychiatry. 2016; 73: 56-63.
18. Benedetti F, Smeraldi E. et al. Curr Pharm Des. 2009; 15: 2637-2649.
19. Terman JS, et al. Arch Gen Psychiatry. 2001; 58: 69-75.
20. Horne JA, Ostberg O. Int J Chronobiol. 1976; 4: 97-110.
21. Wehr TA, Wirz-Justice A. Pharmacopsychiatria. 1982; 15: 31-39.
22. Canali P, et al. Bipolar Disord. 2014; 16: 809-819.
23. Melloni EMT, et al. J Affect Disord. 2020; 274: 1049-1056.
24. Benedetti F, et al. J Clin Psychiatry. 2014; 75: 133-140.
25. Palagini L, et al. Sleep Med Rev. 2014; 18: 225-235.
26. Morin CM, et al. 1993; 61: 137-146.
27. Xie L, et al. Science. 2013; 342: 373-377.
28. Morin CM, et al. Nat Rev Dis Primers. 2015; 1: 15026.
29. Wassing R, et al. Curr Biol. 2019; 29: 2351-2358.e2354.
30. Riemann D, et al. Sleep Med Rev. 2010; 14: 19-31.
31. Doherty TS, Roth TL. Prog Mol Biol Transl Sci. 2018; 157: 1-19.
32. Michopoulos V, et al. Neuropsychopharmacology. 2017; 42:254-270.
33. Hertenstein E, et al. Sleep Med Rev. 2019; 43: 96-105.
34. Palagini L, et al. J Sleep Res. 2022; 31: e13628.
35. Palagini L, et al. J Clin Sleep Med. 2018; 14: 759-766.
36. Richards A, et al. Neuropsychopharmacology. 2020; 45: 55-73.
37. Saper CB. Continuum (Minneap Minn). 2013; 19: 19-31.

SCHIZOPHRENIA

Targeting trace amine-associated receptors (TAARs) to treat schizophrenia

In this symposium titled 'Novel TAARgets for stabilizing neural circuits in schizophrenia', presented at the 35th ECNP Congress in Vienna, Austria (15th–18th Oct), Prof Christoph Correll (The Donald and Barbara Zucker School of Medicine, New York, USA; Charite Universitätsmedizin, Berlin, Germany) first discussed how both positive and negative symptoms of schizophrenia involve widespread disruptions to a number of neural circuits linking the striatum, limbic system and cortex. Antipsychotics predominantly bind to D2 dopamine receptors and, while helpful for some symptoms, can be associated with a number of adverse events depending on their receptor action profile. Dr Anissa Abi-Dargham (Stony Brook University, UK) introduced trace amines, which are structurally similar to monoamines but function more diffusely, and trace amine receptors, that can heterodimerise with other receptors and influence their functioning. As these include the D2 dopamine receptors, Prof Leslie Citrome (New York Medical College, US) discussed how trace amine associated receptor (TAAR) targeting drugs are being in investigation in patients with schizophrenia and have shown significant changes in positive and negative symptoms with a low adverse event profile.

Targeting neural circuits in schizophrenia can help with unmet needs

Schizophrenia is currently understood to be a disorder of hyperactive dopamine at D2 receptors, hypofunction of the glutamate N-methyl-D-aspartate (NMDA) receptor and cortical hyperfunction of the serotonin 5-HT_{2A} receptor. Changes in neural circuits include those in the mesocortical pathway, due to decreased dopamine and GABA release and $5HT_{2A}$ expression; the mesolimbic pathway, associated with negative symptoms; the mesostriatal pathway, associated with increased dopamine synthesis and release and positive symptoms; and the nigrostriatal pathway, with motor involvement.[1,2]

> *Symptoms of schizophrenia involve complex brain circuitry and not just discrete regions*

It was initially thought that positive symptoms of schizophrenia arose from abnormal functioning of dopamine projections from the midbrain to limbic regions. More recent work though, has shown far wider neurological connections between the striatum and both the midbrain and the cortex, involved in executive functions and sensory motor functions.[3-6] Neuroimaging studies reveal that positive symptoms are linked to dopamine hyperactivity in a circuit starting at the dorsomedial substantia nigra and involving striatal associative and adjacent sensorimotor regions.[2] One study in patients with schizophrenia found significant dopaminergic function increases in the sensorimotor and especially associative regions in the striatum.[7] Striatal connections to other parts of the brain have also been shown altered in frontal areas linked to positive symptom severity.[8] This, said Prof Howes, points to the striatum being one cause of the alterations in functioning in the cortex in patients with schizophrenia.

For over 70 years, dopamine D2 receptor blockade have been the treatment target for schizophrenia.[1] However, around a third of patients do not respond to such antipsychotics, or have persistence of negative and cognitive symptoms.[1] There are also a number of adverse events associated with antipsychotics related to their mechanism of action, which may result in drug non-adherence.[9] Antipsychotic binding to D2 receptors[10] affects the above mentioned pathways in a widespread manner and while mesostriatal pathway blockade may lead to a reduction of symptoms, blockage of other neural circuits, such as the mesolimbic and mesocortical pathways, may actually increase negative symptoms. Additionally, nigrostriatal pathway blockage is associated with myriad adverse events including tremor, rigidity, akinesia, dyskinesia and dystonia, with tuberoinfundibular hypothalamic pathway blockage associated with prolactin elevation, sexual dysfunction, amenorrhea and galactorrhoea.[1,2]

Trace amine-associated receptors (TAARs) as therapeutic targets for schizophrenia

What is needed, according to Prof Howes, are antipsychotics that are more selective to "turn down overactive dopamine but not block it where it's functioning normally." Such drugs in development include trace amine receptor compounds and muscarinic receptor agonists that do not directly interact with dopamine receptors.[10,11]

Trace amines have similar structures to monoamine neurotransmitters but are expressed at far lower levels and are not packaged and released as these neurotransmitters are. They function at trace amine-associated receptors (TAARs), the most characterised of which is TAAR1.[12-15] TAARs occur in several parts of the brain involved in cognitive, emotive and motor circuits. These include the dorsal raphe nucleus; the ventral tegmental area (VTA) and substantia nigra; the hippocampus and subiculum; the globus pallidum; the basolateral amygdala; and several cortical areas.[16] TAAR1 is also expressed in peripheral tissues including pancreatic b-cells, immune systems cells, the liver and the digestive system.[12,14,15] This, postulated Dr Abi-Dargham, means trace amines may affect glucose metabolism, the immune response and gastric emptying.

> *Trace amines work in several brain regions and throughout the body*

The TAAR1 receptor is located intracellularly in both pre- and post-synaptic neurons. It can move to the cell surface and heterodimerise with other receptors including

D2 dopamine receptors, influencing their functioning.[13] For instance, dopamine decrease in hyperdopaminergic regions, such as the nucleus accumbens can be decreased by TAAR1 agonists.[12,15] TAARs also play a role in prefrontal cortex glutamate transmission with TAAR1 agonists shown to suppress non-competitive NMDA receptor blocker-induced hyperlocomotion. This occurs by preventing hypoglutamatergic activity.[12,15] TAARs additionally have a role in balancing 5-HT receptor activity,[12] as it has been evidenced in TAAR1 knockout mice that show increased serotonin levels[13] and how TAAR1 activation can increase 5HT1A receptor agonist potency and TAAR1 blockade can decrease it.[14,16] When the TAAR1 receptor is stimulated with an agonist, dopamine availability can be lowered via decrease in midbrain VTA dopamine neuron activity. TAAR1 agonists can also increase presynaptic D2 autoreceptor inactivation and reduce dopamine-driven behaviours post-synaptically.[13,16]

> *TAAR1 agonists as potential treatments for schizophrenia*

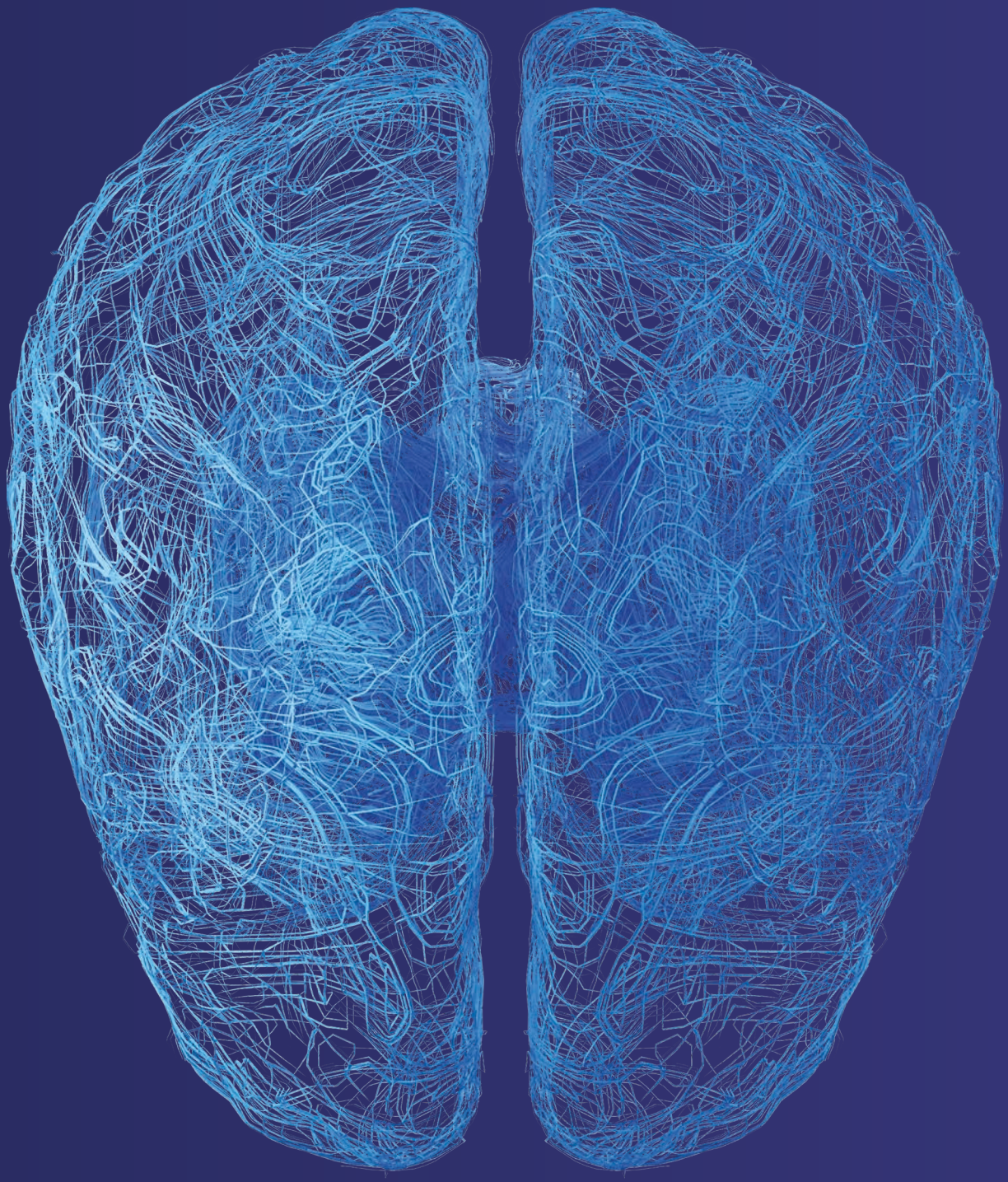
There is a lot of preclinical evidence to support the development of TAAR1 targeting drugs in schizophrenia. This includes that some rare mutations show TAAR1 involvement in patients with schizophrenia and that TAAR1 knockout mice have dopamine increases, similar to that shown in schizophrenia. TAAR1 agonism in animal models also point to antipsychotic-, antidepressant- and pro-cognitive effects as well as prevention of weight gain and fat accumulation related to the use of some antipsychotics.[12,15,17,18]

TAAR1 agonists can lead to improvements in positive and negative symptoms of schizophrenia

Phase II and III studies have been carried out and/or are underway including of a TAAR1 partial agonist[19] and a TAAR1 agonist with $5HT_{1A}$ agonist activity.[20]
One randomised, placebo-controlled, clinical trial in patients aged 18–40, who were predominantly male (around 64%) and white (around 81%) found Positive and Negative Syndrome Scale (PANSS) scores significantly decreased after 3 and 4 weeks' treatment with a response rate (PANSS improvement ≥20%) of 64.6% with the TAAR1 agonist and 44.0% with the placebo. There were also significant effects on positive and negative subscales and on depression ratings.[21] Improvements continued over 26 weeks follow-up.[21,22] Adverse events included low incidences of somnolence, agitation, extrapyramidal symptoms and nausea with discontinuation because of an adverse event being 8.3% for the TAAR1 agonist and 6.4% for the placebo.[21] There were also minimal changes in weight, metabolic indices and prolactin levels over 26 weeks.[22]

Educational financial support for this Satellite symposium was provided by Sunovion Pharmaceuticals, Inc.

1. Correll CU, et al. J Clin Psychiatry. 2022; 83 (1).
2. McCutcheon RA, et al. Trends Neurosci. 2019; 42: 205-220.
3. Lewis DA, Lieberman JA. Neuron. 2000; 28: 325-334.
4. Howes OD, Kapur S. Schizophr Bull. 2009; 35: 549-562.
5. Brunelin J, et al. Curr Med Chem. 2013; 20 :397-404.
6. Stępnicki P, et al. Molecules. 2018; 23: 2087.
7. McCutcheon R, et al. Schizophr Bull. 2018; 44: 1301-1311.
8. Horga G, et al. JAMA Psychiatry. 2016; 73: 862-870.
9. Dibonaventura M, et al. BMC Psychiatry. 2012; 12: 20.
10. Lobo MC, et al. Neurosci Biobehav Rev. 2022; 132: 324-361.
11. Kaar SJ, et al. Neuropharmacology. 2020; 172: 107704.
12. Nair PC, et al. Mol Psychiatry. 2022; 27: 88-94.
13. Gainetdinov RR, et al. Pharmacol Rev. 2018; 70: 549-620.
14. Dedic N, et al. Int J Mol Sci. 2021; 22: 13185.
15. Dodd S, et al Neurosci Biobehav Rev. 2021; 120: 537-541.
16. Berry MD, et al. Pharmacol Ther. 2017; 180: 161-180.
17. Revel FG, et al. Mol Psychiatry. 2013; 18: 543-556.
18. Rutigliano G, et al. Cell Mol Neurobiol. 2020; 40: 239-255.
19. Hoffmann-La Roche. Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of RO6889450 (Ralmitaront) in Patients With Schizophrenia or Schizoaffective Disorder and Negative Symptoms. https://clinicaltrials.gov/ct2/show/NCT03669640?term=NCT03669640&draw=2&.... Published 2022. Accessed: 30 Oct 2022.
20. Sunovion. A Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Adults With Schizophrenia. https://clinicaltrials.gov/ct2/show/study/NCT02969382?term=SEP-363856&ph.... Published 2021. Accessed: 30 Oct 2022.
21. Koblan KS, et a;. N Engl J Med. 2020; 382: 1497-1506.
22. Correll CU, et al. NPJ Schizophr. 2021; 7: 63.



ALZHEIMER'S DISEASE

Assessing clinical outcomes in Alzheimer's disease

Clinical outcomes are vital to assess a person with Alzheimer's disease (AD) and track their progress. In this symposium, held at the 8th Congress of the European Academy of Neurology, Vienna, June 24–28 2022, Dr John Harrison (Alzheimer Center of the VUmc, Amsterdam, The Netherlands), discussed how the Clinical Dementia Rating scale is a comprehensive assessment of dementia, but content validity might be variable. Dr Temitope Farombi (Chief Tony Anenih Geriatric Center, University College Hospital, Ibadan, Nigeria), discussed use of the quick to administer Mini-Mental State Examination, and highlighted how the Identification and Intervention for Dementia in Elderly Africans measure may be more suitable in people with low formal education levels. Dr Rui Araújo (Centro Hospitalar Universitário São João, Porto, Portugal) talked about the Montreal Cognitive Assessment, which is used as a screening test. While advantages include sensitivity to early stage AD, there are high false positive rates in culturally diverse populations. Finally, Professor Ramin Nilforooshan (Dementia Research Institute, Imperial College London, UK) highlighted the use of digital biomarkers to track changes in the health of people with AD and how these may be used in the future to alert people to early health concerns in this realm.

The Clinical Dementia Rating Scale

The Clinical Dementia Rating (CDR) scale is an hour long, semi-structured interview with the patient and a caregiver. It includes assessment in six domains: memory; judgement and problem solving; orientation; home and hobbies; personal care; and community affairs, as well as having a global score.[1] Scores on these domains, from 0–3 for normal to severe with a 0.5 score for 'questionable,' are independent of each other and level of impairment may differ between each domain.[2]

> *The Clinical Dementia Rating scale is a comprehensive, semi-structured interview*

Though useful, the CDR is rarely applied in clinical practice, reported Dr Harrison, and discrepancies have been found between naïve and experienced raters regarding the severity of dementia.[3] Overall, Dr Harrison concluded the while it may be useful, the CDR, in his opinion, has variable content validity, variable reliability, and modest sensitivity.

The Mini-Mental State Examination and Identification and Intervention for Dementia in Elderly Africans measure

Dr Farombi discussed the Mini-Mental State Examination (MMSE),[4] which is often used as a quick screen in the clinic[5] as it takes around 5–10 minutes to administer,[6] and as a secondary endpoint in clinical trials.[7] The MMSE quantitively assesses cognitive impairment severity[6] and can be used to classify moderate stages of dementia.[8] Assessments include of orientation, attention or calculation, registration, recall, language, comprehension, and motor skills.[6] Possible total scores range from 0–30 with a score ≤23 indicating dementia.[4]

The MMSE is fast and easy to administer and scoring is straightforward; however, it doesn't assess executive functioning and it may not be sensitive to subtle cognitive changes in patients with early dementia or mild cognitive impairment (MCI).[4,6] Importantly, highlighted Dr Farombi, MMSE performance outcomes are affected by education level,[4] and there are few local language translations.

> *The Identification and Intervention for Dementia in Elderly Africans is of use for people with low formal education levels*

The Identification and Intervention for Dementia in Elderly Africans (IDEA) is a 10–15 minute instrument with three domains: naming, language and abstract thinking; orientation; and memory and praxis. Total score is 15 with a score ≤7 indicating major cognitive impairment. IDEA, currently validated in Tanzania and Nigeria,[9] shows good inter-rater reliability and internal consistency and performs well in comparison to similar tests in populations with low formal education levels.[9,10]

With these results in mind, Dr Farombi asked, "should we continue to use MMSE alone or look at it holistically and combine different cultural biases and environmental and education backgrounds in making a clinical trial design that's inclusive?"

The Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a 10–15 minute screening test that is available in many languages. This 30-point test investigates concentration, orientation, focus and spatial awareness, language and recall, and includes the clock-drawing test. A score ≤25 indicates dementia risk.[11,12] The MoCA is used as a secondary endpoint in clinical trials[7] but less often in clinical practice[11] as it may be more challenging for patients and requires training and certification to use.[13]

> *The Montreal Cognitive Assessment is a quick screening test to assess dementia risk*

According to Dr Araújo, the MoCA is not only a helpful and relatively comprehensive 'bedside' instrument, but also useful for uncovering 'hidden' cognitive impairments and for patients with co-pathologies. Advantages to the MoCA include that it is fast to administer and, compared to the

MMSE, covers additional cognitive domains and is more sensitive in early-stage AD and MCI. However, it doesn't assess some cognitive domains relevant to AD, such as apraxia, it can only be administered by a trained healthcare professional, and there are high false positive rates in culturally diverse populations.[11,14]

Digital biomarkers

Digital biomarkers include mobile and wearable devices and applications that can actively and passively collect health data. Such devices can monitor changes in domains that may be relevant to AD progression. As these devices are increasingly being used in the general population, they might prove useful in charting and recognizing cognitive, behavioral, sensory, and motor changes years before otherwise noticeable MCI or mild AD.[15]

However, highlighted Professor Nilforooshan, a number of issues need to be addressed before digital biomarkers can be widely used. For instance, how accurate and cost-effective devices are, how digital data should be integrated with clinical data, and who should have access to it.[16,17]

> *Digital biomarkers may be used in the future to alert to early Alzheimer's disease-related changes*

The 'Healthy Home' initiative, being carried out at the Dementia Research Institute at Imperial College London, UK, gives patients simple biometric devices that can measure, for instance, blood pressure, temperature, gait, and walking speed. The devices show changes in an individual's biometric measures so they can be contacted if something adversely changes. This, said Professor Nilforooshan, means a patient can be seen at a clinic when needed, instead of having to have regular, scheduled check-ups that may be too near or too far apart for each person's needs.

1. Morris JC. Neurology. 1993; 43: 2412-2414.
2. Cedarbaum JM, et al. Alzheimers Dement. 2013 ;9(1 Suppl): S45-55.
3. Tractenberg RE, et al. Alzheimer Dis Assoc Disord. 2001; 15: 155-161.
4. Dementia Care Central. Mini-Mental State Exam (MMSE) Alzheimer's/Dementia Test: Administration, Accuracy and Scoring. Available at: https://www.dementiacarecentral.com/mini-mental-state-exam/. Published 2020. Accessed: 8 July 2022.
5. Mitchell AJ. J Psychiatr Res. 2009; 43: 411-431.
6. Folstein MF, et al. J Psychiatr Res. 1975; 12: 189-198.
7. Evans S, et al. Eur J Epidemiol. 2018; 33: 635-644.
8. Benoit JS, et al. Am J Alzheimers Dis Other Demen. 2020; 35: 1533317520918719.
9. Paddick SM, et al. BMC Geriatr. 2015; 15: 53.
10. Gray WK, et al. J Geriatr Psychiatry Neurol. 2014; 27: 110-118.
11. Nasreddine Z. MoCA Cognitive Assessment. Available at: https://www.mocatest.org/faq/. Published 2022. Accessed: 8 July 2022.
12. Dementia Care Central. Montreal Cognitive Assessment Test (MoCA) for Dementia & Alzheimer's. Available at: https://www.dementiacarecentral.com/montreal-cognitive-assessment-test/. Published 2020. Accessed: 8 July 2022.
13. Trzepacz PT, et al. BMC Geriatr. 2015; 15: 107.
14. Thomann AE, et al. J Alzheimers Dis. 2018; 64: 643-655.
15. Kourtis LC, et al. NPJ Digit Med. 2019;2: doi: 10.1038/s41746-019-0084-2
16. Bent B, et al. J Clin Transl Sci. 2020; 5: e19.
17. Ku JP, Sim I. NPJ Digit Med. 2021; 4: 83.

ANXIETY

How to accurately identify social anxiety disorder

Professor Borwin Bandelow sat with us to talk about social anxiety disorder and its debilitating impact on the lives of those with the condition.

When diagnosing social anxiety disorder, Professor Bandelow recommends differentiating it from other closely related anxiety disorders, such as panic or generalized anxiety disorders, as well as psychotic disorders such as schizophrenia. Since people with social anxiety disorder may rely on alcohol to relieve social anxiety, he also recommends screening for substance abuse disorders. Finally, Professor Bandelow cautioned that people with social anxiety disorder may be at increased risk of isolation because of the COVID-19 pandemic.

> *"People with social anxiety disorder have a fear of social situations and being judged unfavourably, going beyond shyness and impacting on their social and occupational functioning and quality of life."*

What is social anxiety disorder?

People with social anxiety disorder have fears in situations where they are the center of attention and they have the feeling they could be criticized by other people. This is why they avoid social situations like meeting unfamiliar people or test situations, performance situations where other people could speak negatively about them.

Social anxiety disorder is not only shyness. It's more than that. Because some people with social anxiety disorder have difficulties to find a partner, to find a good job because in job assessments, they do not perform well or at school and at examinations they have difficulties, and this affects their quality of life.

> *"Social anxiety disorder is not only shyness. It's more than that."*

What is the social anxiety disorder?

When patients come to me, they say: "I have these terrible fears in social situations. That means I'm trembling. I'm blushing. My hands are shaking and I have palpitations." This is why they fear these situations. They don't want to go to a restaurant because they think they are being observed in the restaurant. They don't want to go to tests and to speak to unfamiliar people.

What are the main challenges in diagnosing social anxiety disorder?

The people who have SAD could complain about panic attacks because they have panic attacks in social situations and then we have to check if it's panic disorder or social anxiety disorder. The difference is that the people with panic disorder think they have some somatic condition, some cardiac disease or neurological disorder.

People with social anxiety disorder, they know perfectly well why their heart is beating and why they are shaking because they know, "I'm afraid of this situation."

We also have to differentiate social anxiety disorders maybe from psychotic disorder. If a patient tells you he has the feeling of being observed by other people then you have to differentiate: Is this a psychotic disorder like schizophrenia or is it only social anxiety disorder, where people think that they're ugly or they don't behave well and the clothing's not right so other people might laugh at them? This is what people with SAD feel.

> *"Sometimes all the anxiety disorders overlap. It means people with SAD may also have GAD but also we can have an overlap with substance abuse disorder"*

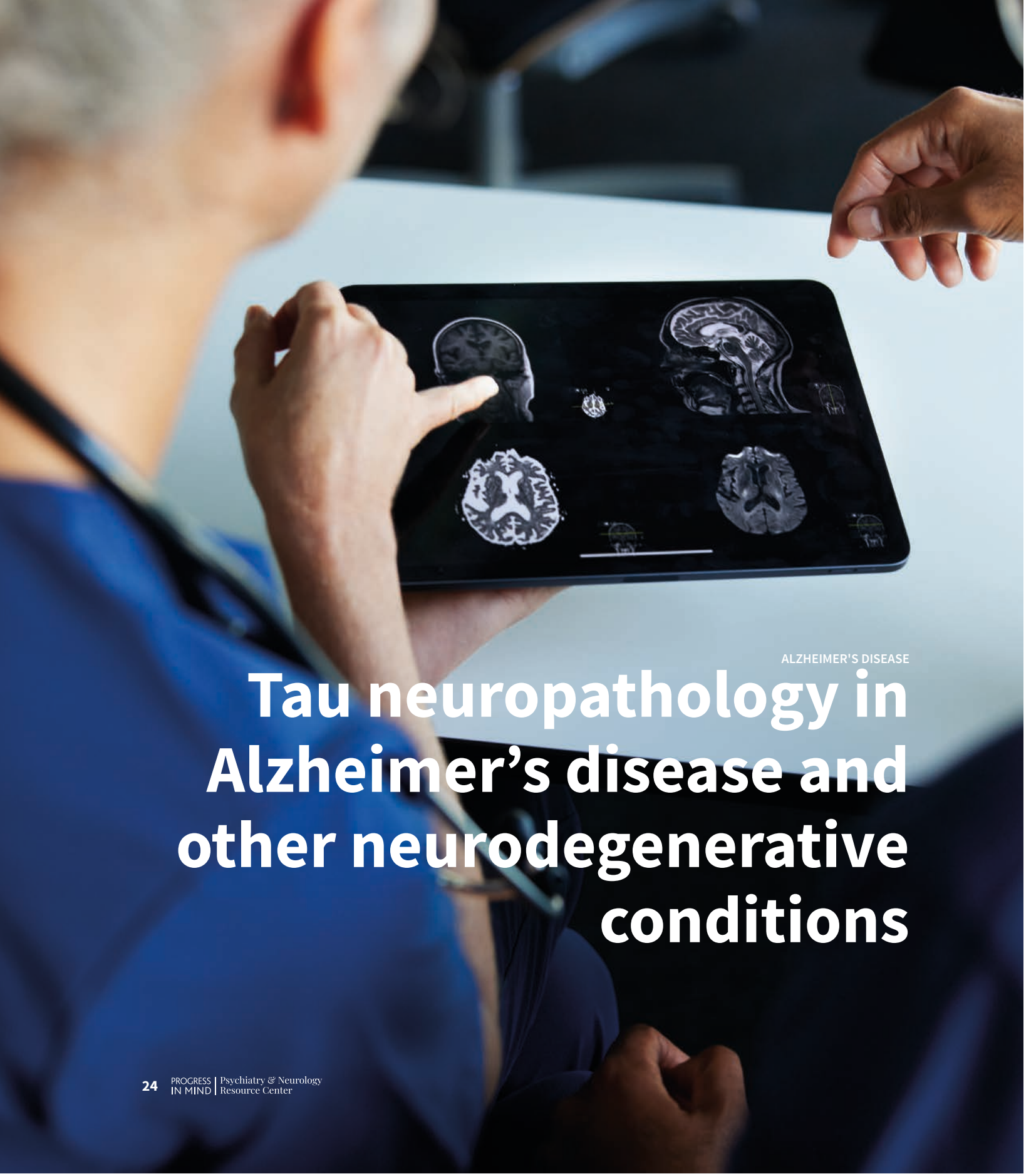
Sometimes all the anxiety disorders overlap. It means people with SAD may also have GAD but also we can have an overlap with substance abuse disorder because alcohol relieves social anxiety and this is why people start social drinking. And this is why many, many people with SAD develop alcohol use disorder which might be a big, big problem in many of these patients.

> *"We can have an overlap with substance abuse disorder because alcohol relieves social anxiety and this is why people start social drinking"*

How has COVID-19 affected people with social anxiety disorder?

People with social anxiety disorder always used to avoid gatherings of people. And now, with the COVID-19 pandemic, this has increased. That means that many patients have more social isolation than before but some patients with SAD say: "There are no parties anymore. No problem, because I didn't go to parties anyway."

But in the end, this means they do not meet other people and this is even worse than before the pandemic.



ALZHEIMER'S DISEASE

Tau neuropathology in Alzheimer's disease and other neurodegenerative conditions

In this symposium titled 'Human Neuropathology: Tau, a key protein in the human brain,' Dr Corey T. McMillan started with discussion of TAR DNA-binding protein 43 (TDP-43) proteinopathy staging and subtyping then Dr Sònia Sirisi Dolcet presented data regarding how in Alzheimer's disease (AD), occurrence of synaptic oligomeric tau may be an early event. Dr Jennifer S. Rabin then discussed how cognitive decline may arise from interactions between cerebral amyloid angiopathy (CAA) and parenchymal amyloid-beta (Aβ) and Dr Frederique J. Hart de Ruyter presented data on the assessment of retinal phosphorylated tau (p-tau) and Aβ in neurodegenerative diseases. Next, Dr Jamie M. Walker discussed the use of Nanostring Digital Spatial Profiling (DSP) to detect protein expression in the hippocampus in people with AD compared to those without and the symposium ended with Dr Brian D. Hitt showing data from his work on developing antibodies to detect tau seeding in ***"in vitro"***cells and brain tissue.

TDP-43 proteinopathies: Subtyping and staging

TDP-43 proteinopathies have different neuropathological staging patterns that, according to Dr McMillan, do not completely account for mixed neuropathology.[1,2] Subtype and Stage Inference (SuStaIn) is an algorithm to aid disease progression modelling that attempts to identify temporal and spatial TDP-43 spread utilising brain cross-sectional 'snapshots' from imaging data.[3] Dr McMillan's study compared SuStaIn staging utilising ordinal (0–3+) neuropathological ratings in 21 anatomic regions.

In amyotrophic lateral sclerosis (ALS), a pattern of staging was identified whereby pathology first develops in the spinal cord then spreads to the medulla and motor cortex then the frontal, angular and temporal cortices. There was some uncertainty in the model in early stages. In frontotemporal lobar degeneration (FTLD), there was more model certainty, especially in the middle stages of disease where there was a widespread pattern of progression. In limbic-predominant age-related TDP-43 encephalopathy (LATE) ±AD, in early stages there was more model certainty. Here, pathology was shown in the amygdala, which then spread through medial temporal lobes, then the anterior cingulate, orbitofrontal cortex then lateral temporal cortex. Both similarities and differences were found between FTLD and LATE.

> *The SuStaIn algorithm can help model TDP-43 proteinopathy staging*

The SuStaIn outputs relative to neuropathological standards for staging showed generally good correlation except for ALS, where there was some uncertainty. Whereas with some standard staging methods around 12% of FTLD cases do not fit the pattern,[1] with SuStaIn, the majority did fit. Additionally found were potential subtypes of ALS and FTLD and homogenous LATE progression.

Early synaptic oligomeric tau may occur in Alzheimer's disease

P-tau accumulation has been shown both pre- and post-synaptically in people with AD.[4] Dr Dolcet discussed how tau seeds generated by different phosphorylated oligomers may precede tangle formation[5] and asked if synaptic oligomeric tau could be an early event in AD. Her work utilised array tomography on serial sections of superior temporal and primary visual areas in healthy controls (n=24; mean age 78.12) and people with sporadic AD (n=29; mean age 83.69, Braak stages V–VI).

> *Tau seeding can occur early in Alzheimer's disease both synaptically and post-synaptically*

A decrease in excitatory synaptic density was found in people with AD compared to controls, correlating with dystrophic neurites. P-tau and P22+ oligomeric tau was found to colocalise with synaptophysin in synapses. P22+ oligomeric tau forms were found in the synapse in AD cases including globular oligomers in dystrophic neurites and fibrils in the synapse and post-synaptic terminals.

Oligomeric tau was also found in regions without AD-relevant pathology. In the temporal cortex there was a positive correlation between oligomeric tau and neurofibrillary tangles (NFTs); however, synaptic oligomeric tau was found to precede NFT presence. Though less dense post-synaptically, the presence of oligomeric tau in these regions suggested, said Dr Dolcet, that trans-synaptic tau seeding could be possible. She also concluded that pathological tau forms appearing early in AD may be a future therapeutic target.

A potential link between vascular burden and Alzheimer's disease pathology

CAA occurrence, with a build-up of amyloid in the cerebrovasculature, increases the risk of AD.[6] Dr Rabin's study aimed to examine the relationship between CAA, tau deposition, cognitive decline and parenchymal Aβ burden and assess whether the association between CAA and cognitive decline is mediated by tau burden. The cohort included participants with no/mild CAA (n=1101; mean age at death 89.9; 39.1% with dementia) or moderate/severe CAA (n=621; mean age at death 90.5; 56.0% with dementia). Prior to death, cognition was assessed annually for a mean of 8.8 years.

> *Cognitive decline in Alzheimer's disease may be exacerbated by both cerebral amyloid angiopathy and Aβ burden*

A positive association was found between CAA and neuritic plaque burden, that decreased in the severe CAA groups, and between CAA and tau burden. When stratified by Aβ burden, there was no relationship with CAA in tau in low plaque cases, but there was in higher plaque cases. Correlations were found between CAA, Aβ burden and cognitive decline, which, said Dr Rabin, suggested the former two may promote the latter. In participants with a high plaque burden, the association between CAA and cognitive decline was postulated to be tau mediated. This may mean, discussed Dr Rabin, that CAA accelerates tau burden, that may in turn affect vasculature, necessitating both pathologies to be therapeutically targeted.

Could retinal p-tau and Aß be utilised in neurodegenerative disease assessment?

Dr Ruyter discussed the need for easily accessible, patient friendly, low cost biomarkers in AD. Neurons in the retina can be directly visualised in a non-invasive way and his studies aimed to assess post-mortem Aβ presence and tau pathology in the retina of people with neurodegenerative diseases (n=46; mean age 71.0) or cognitively normal controls with (n=10; mean age 83.4) or without (n=6; mean age 56.5) Braak neuropathology. Retinas were digitally analysed to assess mean surface area with immunoreactivity to early and late stage disease p-tau antibodies.

> *Retinal p-tau may help predict brain p-tau burden*

Only in three cases was Aβ detected in the retina, including one AD case, no plaques were observed. Depending on the epitope, p-tau showed a diffuse signal in AD cases compared to none in controls. There were significant differences in quantification of p-tau between AD cases (n=17) and controls and other tauopathies (n=9) and controls. P-tau was only found in the retina in the far and mid periphery regions, not the central region. It was also found that when p-tau in the retina was low, so was p-tau in the brain. However, this was not necessarily vice versa leading Dr Ruyter to conclude that retinal p-tau as a biomarker was specific but not sensitive.

Using spatial proteomics to ascertain differences in hippocampus neuropathology in Alzheimer's disease, primary age-related tauopathy and 'resistant and resilient' individuals

Dr Walker discussed Nanostring DSP. Here, protein expression with 73 UV-photocleavable oligo-conjugated antibodies ('multiplex technology') in hippocampal sections (CA1, CA2, entorhinal cortex) were examined with 18 regions of interest per slide including neurons with or without NFTs and the immediate neuronal microenvironment. Protein expression was examined in people with AD or primary age-related tauopathy (PART) compared to those without ('resistant' and 'resilient' cohorts).[7]

> *Protein expression levels differ between people with or without Alzheimer's disease or primary age-related tauopathy*

Dr Walker found a correlation between NFTs in neurons and increased expression of Ab-processing and tangle-located proteins, which, she postulated, "reinforces the assumption that tangle and plaque pathology may develop synergistically in AD." Also shown was significantly higher expression in the 'resilient' and 'resistant' cases of proteins involved in misfolded protein degradation, myloid processing, neuronal integrity maintenance and cholesterol removal.

1. Brettschneider J, et al. Nat Rev Neurosci. 2015;16(2):109-120.
2. Nag S, et al. Neurology. 2017;88(7):653-660.
3. Young AL, et al. Nat Commun. 2018;9(1):4273.
4. Spires-Jones TL, Hyman BT. Neuron. 2014;82(4):756-771.
5. Dujardin S, et al. Nat Med. 2020;26(8):1256-1263.
6. Charidimou A, et al. Neurol Neurosurg Psychiatry. 2012;83(2):124-137.
7. Walker JM, et al. Acta Neuropathol Commun. 2022;10(1):23.
8. Mirbaha H, et al. E-life. 2018;7.

In PART and 'resistant' cases there were higher levels of microglia markers. Dr Walker concluded that 'resistance' and 'resilience' may be linked to higher expression of protective proteins and neuronal integrity.

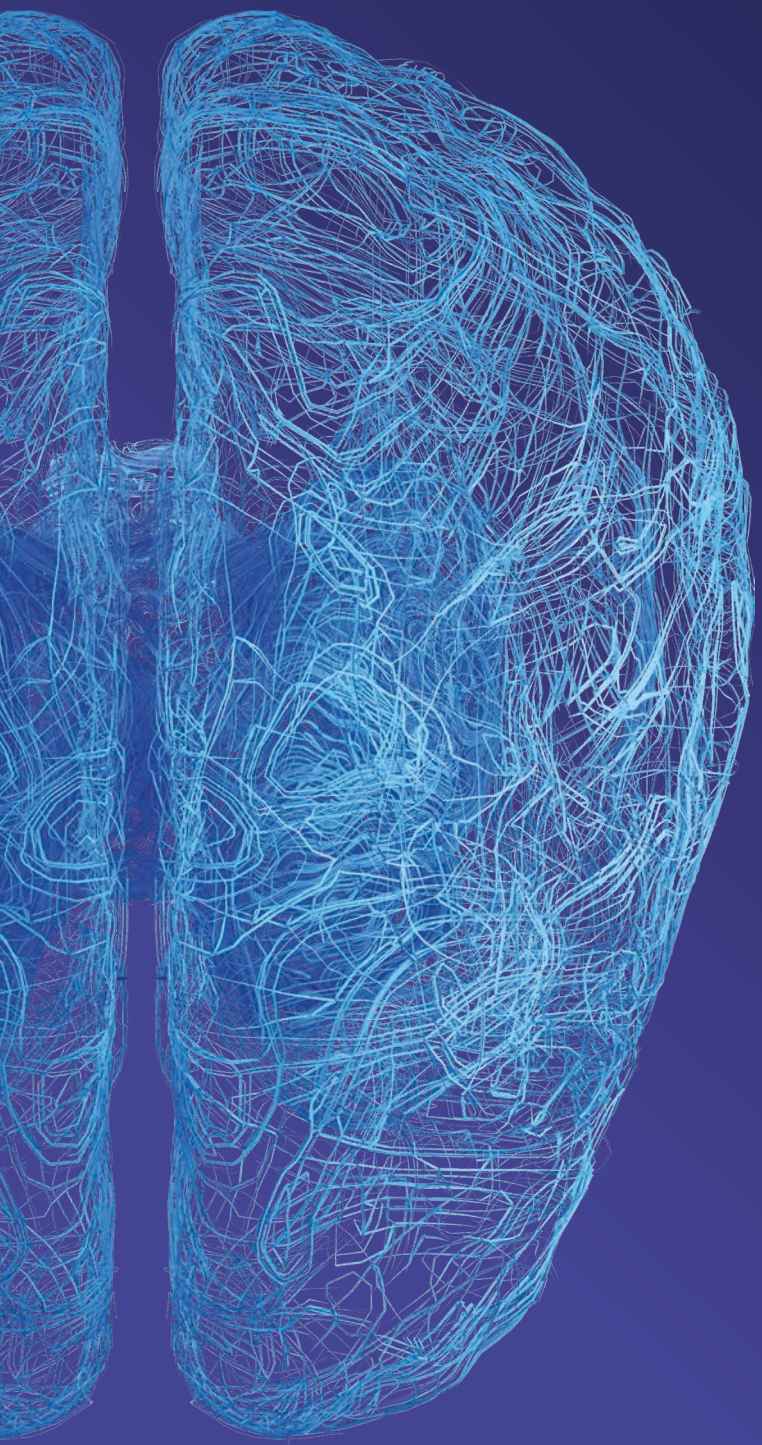
Developing antibodies to detect tau seeding in Alzheimer's disease and other tauopathies

Previous work shows that even tau monomers can be seeds, with a hairpin domain within the R2 repeat domain end terminal being key.[8] Tau seeding has been detected by Dr Hitt using a biosensor Förster Resonance Energy Transfer (FRET) assay. Here, the repeat domain of tau is coupled to a biosensor such that a FRET signal is produced when tau seeds enter an in vitro cell and trigger aggregation. This can be visualised and can be quantified using flow cytometry. Dr Hitt aimed to make monoclonal antibodies to linear peptide antigens in the R1–R2 and R1–R3 transitions of the repeat domain, substituting in a fluorinated proline residue that favours seeding confirmations.

Following antibody generation, the most sensitive and specific forms were selected for detecting AD versus non-AD tauopathies, named MD2.2 and MD3.1. While in control brains there was no seeding activity, in AD brains, most of the seeding activity was found in the immunoprecipitate, showing the antibodies efficiently bind tau seeds. In Progressive Supranuclear Palsy (PSP) brains, this was similar but in Corticobasal degeneration (CBD) and Pick disease (PiD) brains, most of the seeding activity was left in the supernatent so the antibodies were not as sensitive in binding tau seeds.

> *Antibodies to tau seeds can reveal neuropatholgical differences between tauopathies*

Tissue staining showed MD2.2/MD3.1 in the AD cases in perinuclear granular aggregates without neuritic fibrils, with a smaller amount shown in PSP cases and little staining in PiD or CBD cases. In conclusion, the antibodies MD2.2 and MD2.1 were shown to be novel anti-tau agents targeting seed-compentent but not inert tau, predominantly in AD and PSP cases. These may be useful as tools for studying tau seeding in brain tissue.



Progress in Mind keeps you up to speed with the fast-moving world of psychiatry and neurology through knowledge, news and the latest advancements. Get access to global and local insights, perspectives and best practices - no matter where you are.

Read more at progress.im

Lundbeck