

"Genetic and synaptic mechanisms for chronic pain and mood disorders"

Min Zhuo

University of Toronto, Canada

Mental Health Symposium 2026

Thursday, June 25

[2026/06/25 07:02] Carolyn Carillon: Hello everyone.

Today's presentation is being transcribed so those without audio or who require text only can participate in real time.

A little explanation about this service.

Voice-to-text transcriptionists provide a translation of the key ideas discussed, NOT a word for word transcription.

Voice-to-text services provide an in-the-moment snapshot of ideas and concepts, so that those who are unable to hear or to understand the audio program are able to participate in real-time.

You will see the transcription in local chat.

Transcription is provided by Virtual Ability, Inc.

The transcriptionists are

Elektra Panthar

Carolyn Carillon

The following initials in the transcription record will identify the speakers:

MZ: Min Zhuo

[2026/06/25 07:02] Gentle Heron: Good morning, audience. Welcome to Virtual Ability's 2026 Mental Health Symposium.

This is the fifteenth annual occurrence of this conference – we are so proud of that!

The theme this year is PAIN.

Looking at the topics of mental health and pain together is very important, not just for people with disabilities, but for everyone.

Did you know that at any time almost 1.2 billion people across the world are living with a diagnosable mental health disorder?

And a Harvard study estimated that half of the world's population will develop at least one mental health disorder in their lifetime.

(Let me know if you want a link to this study or others I reference and I'll be happy to share them!)

As for pain, of course everyone experiences it from time to time. Acute pain is short term, usually caused by an injury, illness, or surgery.

When that pain occurs almost daily for three months or more, we call that Chronic Pain.

And of course, it's not uncommon for everyday acute pain to develop into chronic pain.

Over 1.5 billion adults worldwide experience chronic pain. That's 20-30 percent of us.

And 10 percent or so have chronic pain so severe that it limits their ability to work, participate in their community, or even take care of themselves.

You all realize the importance of these topics, or you wouldn't have come to this conference.

Today's outstanding lineup of international presenters and panelists will help us explore the causes, impacts, and potential treatments for the intersection of pain and mental health conditions.

I'm sure we will learn quite a lot during today's sessions.

Now a quick housekeeping reminder for this conference.

Many of our presenters are new to Second Life. Please be patient with them.

Hold your thoughts and questions until they are done presenting, because they need to concentrate. Thank you.

Rose, please come up and introduce our first presenter.

[2026/06/25 07:05] Rose Dust: Hello. I am Rose Dust, or Jill.

I have degenerative disc disease and spinal stenosis. I also have mental health disabilities.

I have found a supportive home here at Virtual Ability, and also found many friends and lots of educational opportunities.

I am grateful for Virtual Ability and their work! I feel privileged to be here today as an introducer to one of their speakers.

Our next speaker is a scientist whose work has reshaped how we understand the relationship between chronic pain and mental health.

Dr. Min Zhuo is an internationally recognized pain neuroscientist, Emeritus Professor at the University of Toronto, guest professor at Fujian Medical University in China, and Chief Scientist at Forevercheer Medicine.

His research spans genetics, electrophysiology, pharmacology, and behavior — all aimed at uncovering how chronic pain and psychiatric conditions intersect in the brain.

Please join me in welcoming Dr. Zhuo, whose groundbreaking work continues to open new pathways for treatment, healing, and hope.

[2026/06/25 07:07] Carolyn Carillon: MZ: hello everyone

It's my pleasure to be here to share what I've learned about ...

Can you see the slide?

How do we feel pain?

Acute pain & chronic pain can be different

I'll share what I've learned

When we had progress in neuroscience, the idea of pain has been exploited

One of the French philosophers, Descartes, explored the idea of the pathways of pain

How pain is transmitted into the spinal cord

How it enters the brain and cortex

I'll tell you about one particular area in the brain that contributes to pain

Including emotional pain

I'll explain it

In this slide, you can see a classic Chinese experience

On the other side, you can see an artist, Frida Kahlo, who experienced pain her whole life

We don't have appropriate treatment for pain

Statements of Patients Seeking New Treatment Options

"To say he is in chronic pain would be an understatement. He is so very miserable because of his chronic pain. I have taken him to every doctor and had every test done but we cannot come up with a cocktail of drugs to ease his pain nor a real satisfactory answer to give my father comfort as to where his pain is originating. Needless to say he has a lot of health

reasons to be in pain but as a result of the pain, he is starting to get very tired with living. If you could direct me to anyone or any drug that could assist with his chronic pain I would really appreciate it."

"I am an actress in Canada and I have just read an article regarding your work in the Vancouver Sun newspaper. I am contacting you with regard to my mother who suffers from terrible neuropathic pain, specifically, pudendal neuralgia. In spite of large amounts of medication she has a low quality of life and has lost a tremendous amount of weight due to her pain. I know that it will take a long time for drugs to be developed based on the evidence of the enzyme protein kinase M ζ , but I am wondering if you have any advice for naturally dampening this enzyme's effects, such as through diet? I realize this is unlikely but we are truly desperate. Any advice you can offer would be deeply appreciated."

We are able to see how pain is activated in the brain
And if it's intensity dependent
We now know which parts of the brain are important
More intensity -> more pain
If you apply heat to a person's hand
A person will say ouch
But there's also emotional pain
And that activates the brain as well

We can't cut out the brain from healthy humans, so we use animals
One is a mouse brain
Where we can stimulate pain
Another is a study with monkeys
If you apply cold or hot stimuli to the monkey's face, the pain centers in the brain activate
The brain is important for encoding pain
Pain-related neurons in the human cingulate cortex

W. D. Hutchison et al. Nature Neurosci (1999)
In this slide, on the left, you can see the spinal cord because that's where pain is first transmitted
By using pharmacological agent, we know that glutamate is an important transmitter of pain
Why?
It's the most important transmitter in our whole brain
We use it to see these slides, listen to the words I'm saying

Central synapses: excitatory transmission
Spinal cord
Li et al (1999) Nature, 397:161-164
ACC/IC
Wu et al. J Neurophysiol. 2005

[2026/06/25 07:18] Gentle Heron: Click the giver box by the podium to get a handout with full references.

[2026/06/25 07:18] Carolyn Carillon: MZ: If you listen to my talk, you remember pain is important. Some synapses potentiate and will for a long time
LDP is important for long term memory
LTP is a key mechanism for learning and memory

Tim Bliss and Terje Lomo, J Physiol 1973

If we can make LTP bigger, can we make you smarter?

Mice learn more quickly, the more LTP

Neurobiology

Young receptors make smart mice - T. V. P. Bliss

Nature volume 401, pages 25–27 (1999)

<https://www.nature.com/articles/43333>

Young receptors make mice smarter

9.

Enhanced LTP without affecting LTD

Genetic enhancement of learning and memory in mice - Ya-Ping Tang, Eiji Shimizu, Gilles

R. Dube, Claire Rampon, Geoffrey A. Kerchner, Min Zhuo, Guosong Liu & Joe Z. Tsien

Nature volume 401, pages 63–69 (1999)

<https://www.nature.com/articles/43432>

Physiological pain is normal.

Chronic pain is enhanced

And it's linked to learning memory

Maybe you need to suffer to achieve high learning ability

No Pain, No Brains?

“Smart” transgenic mice are sensitive to chronic pain

Wei et al. Nature Neuroscience 2001

In animals, we know, this drug can reduce chronic pain

We can't test in humans

First genetic evidence for forebrain NMDA NR2B and glutamatergic plasticity in chronic pain, but not acute pain

Translation for pain drugs in the brain: NMDA NR2B receptor antagonists as future analgesics

NMDA NR2B as a selective target for chronic pain

Side effects: cognition (not really, seizure side effects)

Pfizer Japan: NR2B and Nagoya

When we suffer pain, our spinal cord and brain are excited

And we form a memory

And that memory will cause pain and anxiety

Peripheral digit amputation induced LTP in the ACC in vivo: adult rats

Wei and Zhuo, J Physiol 2001

Drugs often don't translate into humans because we test on different species

ACC & LTP are bigger in human brain

Roles of NMDA NR2B subtype receptor in prefrontal long-term potentiation and contextual fear memory.

Zhao Toyada Wu Xu et al. Neuron 2005

[https://www.cell.com/neuron/fulltext/S0896-6273\(05\)00689-](https://www.cell.com/neuron/fulltext/S0896-6273(05)00689-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0896627305006896%3Fshowall%3Dtrue)

[6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0896627305006896%3Fshowall%3Dtrue](https://www.cell.com/neuron/fulltext/S0896-6273(05)00689-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0896627305006896%3Fshowall%3Dtrue)

When you suffer an injury, your ACC is over excited

Adult tree shrew ACC 5 hr LTP AC1-dependent - Song et al., 2024, LTP50s

The tree shrews are small mammals native to the tropical forests of South and Southeast Asia. Tree shrews eat fruit. Tree shrews have a higher brain to body mass ratio than any other mammal, including humans, but high ratios are not uncommon for animals weighing less than 1 kg (2 lb). Among orders of mammals, tree shrews are closely related to primates, and have been used as an alternative to primates in experimental studies of myopia, psychosocial stress, and hepatitis

We use this mechanism to discover drugs for chronic pain

Acute pain is important but chronic pain is the one that makes you suffer

We don't want to interfere with acute pain

For example, if you jump into a hot tub, you need to experience pain to keep yourself safe

ACCLTP: chronic pain in the cortex: a synaptic mechanisms to distinguish acute and chronic pain

Mice lacking AC1, the enzyme that acts as a second messenger, acute pain is normal & chronic pain is blocked

[2026/06/25 07:26] Gentle Heron: Knockout mice are genetically modified to be missing a specific gene

[2026/06/25 07:26] Carolyn Carillon: MZ: this is the first time finding a particular gene involved in chronic pain

It's a selective gene

So if we can inhibit it, we won't interfere with other brain functions

Can we find a mouse without or reduced chronic pain if we can find a smart mouse?

AC1 KO Mice Have Normal Acute Pain But Reduced Chronic Pain

Wei et al. Neuron 2002

The problem with many medicines is that they make you sick or addicted

There are two types of LTP in ACC

[2026/06/25 07:27] Gentle Heron: Notice all the international cooperation among researchers!

[2026/06/25 07:27] Carolyn Carillon: MZ: One is post-synaptic

All the changes are at the receiver site

When we manipulate that site, we can change the amount of pain you suffer

On the other side, you experience pre-LTP that causes emotional pain and anxiety

They're linked

Often with patients who have long-term pain, they are anxious

The AC1 gene is important for both forms of LTP

Calcium-calmodulin stimulated AC1 required for ACC LTP

Membrane-bound protein, 120-140 kDa

Only neurospecific AC

Calcium-CaM stimulated, half-maximal stimulation

At 150-200 nM free Ca^{2+}

Liauw et al J Neurophysiol 2005

We have discovered a small compound you can take orally that inhibits AC1

We are testing on different animals

Summary of ACC LTPs

Pre-LTP: KARs Glu release

Post-LTP: NMDARs AMPARs

Bliss Collingridge Kaang Zhuo Nature Neurosci Review, 2016

AC1 as a key target for treating chronic pain/anxiety
2002-2025

Wei et al, Nature Neurosci, 2001

Wei et al, Neuron 2002

Liau and Zhuo, J Neurophysiol, 2005

Li et al., Science, 2010

Wang et al, Science Translational Medicine 2011

Zhuo, Drug Discovery Today, 2012

Qiu et al., Science Signaling, 2013

Koga et al, Neuron, 2015

Chen et al, Nature Communication, 2018

Liu et al. J Neurochemistry 2020

Wang et al. Science Translational Medicine 2011

When we compare mice and human AC1 genes, they are almost identical

Therefore we believe the drug we develop for mice can be used for humans

[2026/06/25 07:31] Carolyn Carillon: Using different species, including human neuronal cell lines

AC1 KO or NB001

On this slide you can see a variety of genes expressed through different organs of your body

Including opioids

Side effects are common for these drugs

The drug we're developing would have fewer side effects

Preclinical, Phase I-III studies for joint pain in old Beagle dogs

Mouse and human AC1

https://www.proteinatlas.org/ENSG00000164742-ADCY1/summary/gene?utm_source=chatgpt.com

https://www.genecards.org/card/ADCY1?utm_source=chatgpt.com

Distribution of drug targets and side effects (e.g., NMDA receptor; opioid receptors; cox 2; VR1)

Distribution Patterns of Target Proteins for Treatments of Chronic Pain

Blank: No data found. + + + + highly expressed or very; + + + strongly expressed or very effluent; + less effluent; 0 no expression. The distribution patterns of some proteins are based on in situ hybridization data. NS: nervous system.

Wang et al. Science Translational Medicine 2011

The drug we're developing could treat all types of pain

What about headaches?

We mimicked headaches in mice

We found that AC1 is also important here

Also with headache-induced anxiety

I hope I'll be able to share new results in 1-2 years

Behavioral study results

NB001 produced potent analgesic effects in an adult rat model

Inflammatory pain and neuropathic pain

Also fear, including PTSD

By using our drugs in mice, it reduces the symptoms

Including fear & long-term depression

We're suspicious because of genes in families

Some is inherited

However, if you have emotional pain, or physical pain for a long time, your fear and anxiety resulting from chronic pain can be unique to you

Additional indications for AC1 gene and NB001: migraine; PTSD; injury-related anxiety; emotional pain; Parkinson's related pain.

We have looked at all types of chronic pain

The brain is the final organ to process pain, we need to treat ACC, not just the spinal cord, for example

AC1 and NB001 for the treatment of anxiety in migraine

Inhibiting neuronal AC1 for treating anxiety and headache in the animal model of migraine

<https://pubmed.ncbi.nlm.nih.gov/37235050/>

This has been my career

I summarize my book in the book Chronic Pain

Published 3 years ago

It's a professional book, but there's more info in that book

Pain research is among the most important for our health and animals' health

It lets us achieve what we want and be happy

AC1 and NB001 for the treatment of depression (PTSD)

Fear memory regulation by the cAMP signaling pathway as an index of reexperiencing symptoms in posttraumatic stress disorder

Hori et al., 2024 Mol Psychiatry PCT filed

<https://pubmed.ncbi.nlm.nih.gov/38409596/>

University of Tokyo With Prof. Kida

Different types of chronic pain; different animals

AC1 KO or NB001

Phase 1 finished; ongoing Phase 2; Phase 3 finished

New patents we filed new PCT in 2025 for PTSD treatment

ACC/IC network: a beginning of mapping pain and consciousness

LTP helps to reduce chronic pain and anxiety

The final goal of biomedical research and development is to reduce human/animals suffering and pain

Every step we do closer to the new medicine, it is beneficial for human beings

Pain interferes with many aspects of our life

We have shown that AC1 is important

[2026/06/25 07:38] Carolyn Carillon: hopefully we can bring our drug to the market to treat pain and anxiety

Thank you!

[2026/06/25 07:38] Roxksie Logan: ('.:.('.'. ♪ .:.'').:.'')

[2026/06/25 07:38] Roxksie Logan: ♪('.'.:.:.*.*☆☆**.:.:.'')♪

[2026/06/25 07:38] Roxksie Logan: ,.':* APPLAUSE !!!! *:'.
 [2026/06/25 07:38] Roxksie Logan: ☆ (,.'':.:.:***☆**':.:.:'.) ☆
 [2026/06/25 07:38] Roxksie Logan: (,.''(,.' 〰 '''.)'''.)
 [2026/06/25 07:38] Carla Heartsong: ty!
 [2026/06/25 07:38] Rose Dust: claps
 [2026/06/25 07:38] Sheila Yoshikawa: thank you!
 [2026/06/25 07:38] Lissena Wisdomseeker (Lissena Resident): thank you!
 [2026/06/25 07:38] Anzu (Annelies Fratica): clap clap
 [2026/06/25 07:38] Martin McWolf (MartinMcWolf Resident): /me claps
 [2026/06/25 07:39] Katie Velvetpaw: Chronic Pain: New Molecular Insights into Pain and Treatment by Min Zhou is available on Amazon in hardcover and Kindle versions

[2026/06/25 07:38] Mook Wheeler: QUESTION: Is there a clinically-noted *length of time* that chronic pain has to be present for, in order for the ACC-LTP process to generate an *exaggerated/deranged* pain memory? And does the exaggerated pain memory disappear from the brain if the physiological source of the chronic pain is removed?

[2026/06/25 07:38] Elektra Panthar: GH: Are you available for questions?
 [2026/06/25 07:39] Gentle Heron: Thank you Dr. Zhuo. Fascinating research. QUESTION- What is involved in translating your experimental results from mice and other animals into experimental information about humans so that appropriate human remedies and treatments can be developed? You are involved in development of human therapies as well as animal experiments, correct?
 [2026/06/25 07:43] Elektra Panthar: MZ: we need to have a lot of funding for that - I've been working on this for 10 years
 You need to find the subjects with precise characteristics, the tests are heavily controlled in case of humans
 Once we have all the permissions we start the drug testing - even after 10 years there's a long way to go
 [2026/06/25 07:44] Gentle Heron: These are called clinical trials, right?
 [2026/06/25 07:47] Elektra Panthar: MZ: Yes, clinical trials
 Usually they can't be done by me because I'm not an expert on that aspect
 You need to raise funds and hire a company expert in that, approved by the government
 About 10 million dollars to have a drug approved. I'm hoping we can speed up the process and make it less expensive
 [2026/06/25 07:48] Gentle Heron: There is information on how clinical trials work on Healthinfo Island to our west. And there are a bunch of clinical trial opportunities listed there also.

[reposting] Carla Heartsong: Question: I find this very interesting, though it seems you stole my brain scan of 2010 :)
 Kidding, I had a tumour (meningioma) protruding in the right dorsal anterior cingulate cortex, so a LOT you told today I can relate to. I'm so glad since 2010 science evolved so much, it covers more and more what I experimentally but involuntary learned. Back then, I felt I knew more than any specialist I met.
 So my question is: what I still miss is the link to memory, especially contextual memory: sounds/smells/emotional state/surroundings. Mine from before 2010 was wiped out OR unreachable (but an entirely intact factual memory). Could this be caused by trauma/fear, which has a deep bidirectional connection with pain?

[2026/06/25 07:41] Elektra Panthar: MZ: Fear and pain have a lot of connection between them

The hippocampus could also be involved

Yes that's possible

I don't have much time to share but I can say this - we have left and right side of the brain, singular cortex in both can form a connection with the hippocampus

Unfortunately trauma and fear can interfere with memories, yes

[2026/06/25 07:50] Carla Heartsong: so that means I didn't go insane :) hehe

Thank you

[2026/06/25 07:51] Elektra Panthar: MZ: I'd like to follow up with you if you'd like, please email me if you're interested

[2026/06/25 07:51] accpain Resident: minzhuo10@gmail.com

[2026/06/25 07:51] Carla Heartsong: yes!

[2026/06/25 07:51] Gentle Heron: Other questions about pain and mental health for Dr. Zhuo?

I think we need to invite him back when he has finished more research.

And please click the box by the podium for his reference list

[2026/06/25 07:51] Elektra Panthar: MZ: Thank you, I want to learn more about this program

[2026/06/25 07:51] Roxksie Logan: that would be wonderful

[2026/06/25 07:51] RøByη SERRασ (EvilPrincess Serrao): nods

[2026/06/25 07:52] Mook Wheeler: Thank you Dr Zhuo :)

[2026/06/25 07:52] Gentle Heron: Second Life is a good way to reach people from all over the world, Dr Zhuo

[2026/06/25 07:52] accpain Resident: great, and thank you

For inviting me

[2026/06/25 07:52] Gentle Heron: It gives you an international audience

And you did a great job of presenting for your first time in Second Life.

We all have our own horror stories about being a newcomer here.

[2026/06/25 07:53] accpain Resident: thank you....

[2026/06/25 07:53] Gentle Heron: We should ask the audience to tell us what country or part of the world they are from.

I know we have several Europeans here

[2026/06/25 07:53] Martin McWolf (MartinMcWolf Resident): Ireland

[2026/06/25 07:53] Carla Heartsong: Belgium

[2026/06/25 07:53] Roxksie Logan: United Kingdom here 😊

[2026/06/25 07:53] ♡ ᵂᵂᵂᵂᵂ ♡ (Andee Cooper): USA

[2026/06/25 07:53] Beth Ghostraven: mid-Atlantic US

[2026/06/25 07:54] Gentle Heron: east coast USA

[2026/06/25 07:54] iSkye Silvercloud (iSkye Silverweb): (upper midwest USA)

[2026/06/25 07:54] Elektra Panthar: Italy

[2026/06/25 07:54] Itico (Itico Spectre): midwest USA.

[2026/06/25 07:54] Lissena Wisdomseeker (Lissena Resident): near NYC

[2026/06/25 07:54] Katie Velvetpaw: midatlantic USA

[2026/06/25 07:54] DrNHellman Resident: east coast USA

[2026/06/25 07:54] Roxie Marten: Land of the mitten aka Michigan

[2026/06/25 07:55] Lloud Laffer: Middleton, Wisconsin USofA

[2026/06/25 07:55] Roxksie Logan: 😊

[2026/06/25 07:55] accpain Resident: impressive

[2026/06/25 07:57] iSkye Silvercloud (iSkye Silverweb): Thank you so much, Dr. Zhuo, for staying up so late to give this really fascinating presentation!

[2026/06/25 07:54] Gentle Heron: QUESTION- How did you come to teach in Toronto, Dr Zhuo? That is far from your home in China.

If there are no more questions, we can thank Dr Zhou, audience.

[2026/06/25 07:56] Carla Heartsong: I've too much questions too lol. But one more question

[2026/06/25 07:57] Gentle Heron: Go ahead Carla

[2026/06/25 07:57] Carla Heartsong: what is according to you the relationship between the ACC and the autonomic nerve system?

(I've dysautonomia since then)

[2026/06/25 07:57] Elektra Panthar: MZ: Thank you, good question

When we have a lot of pain it will also show in our cardiovascular system

Vagal nerve stimulation could help with that

When I was in college in Iowa my professor was studying the stimulation of the vagal nerve

So yes, there's a solid connection between the cortex and the autonomic nerve system

[2026/06/25 07:58] Carla Heartsong: I get an infuse with Magnesium 3 weekly to suppress peripheral neuropathic pain... and also use mindfulness

Per three weeks

Yes dampens synaptic

So yes, receptor

[2026/06/25 07:59] Gentle Heron: Dr Zhuo, I know it is late at night in China now. Thank you for taking the time to join us today.

[2026/06/25 08:00] Elektra Panthar: MZ: yes

Thank you, my pleasure

[2026/06/25 08:00] Gentle Heron: Please be sure to click the blue poster to the left of the stage. It contains notecards and landmarks about the Virtual Ability community.

And stay well hydrated in the heat!

[2026/06/25 08:00] ♡ ᳵᳵᳵᳵ ♡ (Andee Cooper): claps..

[2026/06/25 08:00] Roxksie Logan: /me .:{APPLAUSE}..

[2026/06/25 08:01] Carla Heartsong: .-''-. APPLAUSE APPLAUSE .-''-.

[2026/06/25 08:01] Gentle Heron: Applause!

[2026/06/25 08:01] Anzu (Annelies Fratica): clap clap

[2026/06/25 08:01] Elektra Panthar: speaking of, brb, refilling the water bottles

[2026/06/25 08:01] Katie Velvetpaw: 🎵🎵🎵 APPAWS! 🎵🎵🎵

[2026/06/25 08:01] DrNHellman Resident: thank you!!

[2026/06/25 08:02] Gentle Heron: The next session begins at 8:30am SLT

Take a hydration break now