

**DR VANJA DURIC**  
**'Brain Mechanism Linking Stress and Illness'**  
**Mental Health Symposium June 18<sup>th</sup> 2016**

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[2016/06/18 08:21] Carolyn Carillon: Hi 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 Nearby Chat.

Transcription is provided by Virtual Ability, Inc.  
Your transcriptionists for this session are LoriVonne Lustre and me, Carolyn Carillon.

We will identify the speakers by their names (initials):  
VD: Vanja Duric

[2016/06/18 08:22] Carolyn Carillon: <<transcription starts>>

[2016/06/18 08:31] Gentle Heron: Welcome everyone to Virtual Ability's 2016 Mental Health Symposium. Our theme this year is "Down But Not Out" and of course like all good themes, it can be interpreted many ways. We have 9 fantastic presentations. I'm sure everyone will find something to learn today. I've enjoyed interacting with the presenters.

Please click the brown Virtual Ability poster to the left of the stage to get a notecard about our community, another notecard sharing locations of Symposium-related exhibits and displays on Healthinfo Island to our west, and a landmark to our upcoming SL13B display. The little Symposium poster at the front by the podium contains handouts from our presenters.

I want to thank all the many VAI helpers who worked so hard on this Symposium,

with special thanks for all the hard work of iSkye Silverweb, the conference organizer.

And now, I'll turn the podium over to our first introducer.

[2016/06/18 08:32] PedroLevy Indigo: Hello and welcome to the Virtual Ability Mental Health Symposium.

The title of this session is "Brain Mechanism Linking Stress and Illness".

My name is PedroLevy Indigo.

I was diagnosed in 1999 as a carrier of Bipolar disorder after a long & painful period of losses.

Right now I am trying to cope with new drugs as the old ones do not have effect on my brain.

It gives me great pleasure to introduce to you Dr. Vanja Duric.

Dr. Duric is an Assistant Professor of Physiology and Pharmacology at the Des Moines University in Iowa (US)

where he is doing neurobiology research on brain events that underlie pathophysiology and treatment of mental illnesses, especially major depressive disorder (MDD).

His primary focus is investigating the relationship between the inhibition of a major cellular signaling pathway that is involved in neuronal survival and development of depression.

Dr. Duric is also interested in brain mechanisms that link depression and other neurological or systemic illnesses, such as chronic pain.

Please hold your questions until the talk is over.

Thank you.

[2016/06/18 08:36] LV (lorivonne.lustre): VD: Good morning and thank you for the nice introduction

I am excited to be here. I hope you can hear me well

this is my first time presenting in this format

I have learned a lot

today we will be talking about stress and the mental illness, and the processes involved

Questions at the end are best,

although I will do my best to answer as we go

We will be looking at stress and the relationship between the physical and psychological illness that can arise

What is stress?

- Defined as presence of significant physiological or psychological threat to the organism that results in acute or persistent strain on the body's compensatory systems

Look at these guys in the top right... the one in the pan is likely experiencing more stress

- Body's compensatory mechanisms deviate from and extend normal physiological regulation in order to protect the organism

You may have heard of 'fight or flight' response... how our body prepares / reacts to stress

Stress is an alarm reaction that involves heightened mental and physical state as a response to a stressor, such as environmental condition or a stimulus

Acute stress can be a good thing.

Types of Stress

- Physiological ("Biologic") Stress
- Psychological Stress

Subtypes:

Acute Stress

Episodic Stress

Chronic Stress

Psychological stress can be thought of the everyday kinds of stress

Stress can also be thought of in terms of duration

catching up with my slides

this is the slide I was just talking about

Stress responses and regulation

Here is a diagram of how stress reacts in our bodies

Structures in the brain release stress hormones

which affects the adrenal glands

> release adrenaline

normally a negative feedback loop regulates this

This is what happens in acute stress, and the stress response will shut down

however when the stress response does not shut down it leads to chronic stress as we can see in this slide

Acute Stress > if stress persists > Chronic Stress

- Dysfunctional regulatory mechanisms
- Central Nervous System
- Systemic effects

Chronic stress is not good for us

for example the negative feedback loops do not shut down the production of hormones involved in stress responses

at the bottom left you can see the individual now has multiple things going on

Mechanisms linking stress and illness

We can likely all relate to some of the examples on the slide

increased heart rate and blood pressure, affect on immune system,

disturbance in digestive system

Stress and illness (chronic stress)

This diagram shows the physiological and psychological illnesses that can result from chronic stress

We will talk about these in detail as we go along

Cardiovascular disease (CVD)

Chronic and acute affects

Acute stress Sudden death in vulnerable individuals

- Major risk factors for CVD: High blood pressure, high blood lipids, diabetes, family history, etc.

Recent research: Chronic stress and depression also major risk factors

- o Prolonged exposures to psychological stress is linked to increased incidences of stroke, myocardial infarction, atherosclerosis and coronary artery disease

- PTSD patients: 60% enhanced risk of myocardial infarction or stroke for example

Cardiovascular disease (CVD)

- Chronic stress
  - o Potential biological mechanisms
  - o Potential psychological and behavioural factors

Personality type, diet, habits (smoking), exercise

if stress responses are not regulated well, bad things can happen with your body.

There may be genetic predispositions as well

Inflammatory responses may arise

a number of things may happen based on these factors with the end result of CVD

Bidirectional relationships

Chronic Stress >< Physical Illness >< psychological illness

> psychological illness

for example, physical illness can lead to stress which in turn leads to psychological illness

Gastrointestinal (GI) Disorders

- High stress and anxiety can be linked to:
  - o Abdominal pain
  - o Severe diarrhea
  - o Peptic ulcers
  - o Chronic inflammation of the digestive tract
  - o Irritable bowel disease (IBD)

Comorbid psychiatric illness is very common

IBD patients: Lifetime depression rate of 27%

- General population: Lifetime depression rate of 12-16%

That is quite an increase for IBD patients

Gastrointestinal (GI) Disorders

- Potential mechanisms linking GI and mood disorders:
  - o Alterations in brain regions that regulate emotions and mood
  - o Dysfunctional HPA axis (i.e., poor regulation of stress responses)
- Alterations in Gut – Brain axis
  - o Gut microbiota diversity is reduced by stress (i.e., bacterial composition)
  - o Microbiome can modulate brain activity resulting in altered stress responses and development of depressive behaviors

This is a 2 way street

microbiota is the bacterial composition in the gut

- Increase in pro-inflammatory signaling  
another disorder: Obesity / metabolic disorders
- Obesity is associated with cognitive defects and comorbid mood disorders
- Obesity and depression seem to be correlated in bidirectional manner
  - o Obesity predisposes to development of depression
  - o Depression can significantly increase the risk of developing obesity (e.g., poor eating habits, sugar cravings, etc.)
 think about comfort eating, things like that
- Obesity contributes to development of state of low-grade systemic inflammation
  - o Increased release of pro-inflammatory signaling molecules

#### Neurological Disorders : Stroke

the image in the upper right shows types of strokes

- Different types of psychiatric disorders commonly observed after stroke
  - o Depression and anxiety
  - o Emotional incontinence
  - o Delusions and hallucinations
- Post Stroke Depression (PSD)
  - o Affects ~ 30-50% of stroke patients in 1st year of recovery
 shown to impair recovery and increase risk of suicide  
 We don't really know why
  - o Multifactorial etiology – complex and poorly understood

#### The last one we will look at is Neurological Disorders: Chronic Pain

- Pain processing: Sensory and Affective (emotional) components
- Mental health disturbances often present:
- o Clinical comorbidity with major depression (~30-50%) and anxiety
  - o Depression in general population: ~5-8%
  - Severity of depression is highly correlated with
    - o Duration and severity of pain, number of pain sites, number and frequency of pain days, inhibition of daily functioning, etc.
  - Management of mental aspects of chronic pain usually is not part of the standard initial treatment
- I'll come back to that

How do these physical or systemic illnesses promote development of clinical depression?

We don't really know the answer

#### Depression

- Prevalent, heterogeneous and recurrent mental illness
- High prevalence in USA
  - o 5-8% of general population at any given time
  - Lifetime prevalence in USA
    - o Around 17% of adults will suffer from depression at least once in a lifetime
    - o Females are affected twice as frequently as males
- Antidepressant agents
  - o Partial effectiveness

- o Delayed therapeutic response
- o Side-effects

### Symptoms of depression

At least 5 of the following symptoms have to be present during the same 2-week period:

1. Depressed mood (e.g., one feels sad, empty, helpless, worried)
2. Loss of pleasure (anhedonia) and interest in daily activities
3. Altered eating - significant weight loss or weight gain (“comfort eating”)
4. Altered sleep (insomnia or hypersomnia)
5. Psychomotor agitation (restlessness) or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive guilt
8. Altered cognitive function diminished ability to think or concentrate
9. Suicidal thoughts, planning, and/or attempting suicide

The first 2 are the main symptoms of depression

Suicidal thoughts is the most severe

### Etiology of Depression

Exact causes are unknown, related to chronic stress

- Disease of the Limbic System
- Loss of serotonin and norepinephrine

This diagram shows the limbic system in the brain

- Limbic System
- Regulation of mood
- Cognition
- Emotional responses

emotional responses include fear

Limbic system areas involved with depression

- Hippocampus
  - o Learning and formation of new memory – recall
  - o Hormonal homeostasis – stress responses and part of negative feedback (shown in green)

- Prefrontal Cortex (PFC)
  - o Cognitive and executive functions

the front part of the brain

- Amygdala
  - o Fear responses (shown in red)

Depression pathophysiology: Human subjects

This image shows how the activity is decreased and there is neuronal atrophy especially in areas of the limbic system

similarities between brains of those with PTSD and depression

Depression pathophysiology: Animal studies

Exposure to chronic stress leads to neuronal atrophy and behavioural changes

This can be reversed -- good news

we can develop new neurons, especially in the hippocampus

Comorbid depression

- Mental health disturbances often present in many physical/systemic illnesses
- Clinical comorbidity with major depression and anxiety up to 50%
- o Pain
- o Stroke
- o Cardiovascular disease
- o Obesity
- o Diabetes
- o Cancer
- o Many others

How do chronic pain patients become depressed?

It is very complex

the overall situation can lead to altered pain perceptions. One thing leads to another

Brain response to pain

Sensory pain and affective / emotional aspects of pain

Brain regions involved in pain and depression comorbidity

for example, pain memories can be created

Findings in Animal Pain Models

- Chronic pain induces depressive- and anxiety-like behaviors
- o Anhedonia – lack of pleasure
- o Helplessness
- o Anxiety – avoidance of open spaces
- Hippocampus
- o Decreased neurotrophic factor support
- o Decreased rate of neurogenesis
- o Increased activation of microglial cells (i.e., sign of inflammation)
- o Increased levels of pro-inflammatory molecules  
Interleukin-1 beta (IL-1b)

I have a couple of slides left

Pain and Stress Decrease Hippocampal Neurogenesis

we can see in the middle and far right area that there is a decrease in neuronal development in the hippocampus

Role of IL-1 $\beta$  in Pain and Depression

Challenges to the body can induce the inflammatory response

I think I am almost done

This diagram summarizes what we have been talking about

this is the summary slide

On a positive note... there is some hope in treatment of depression

Ketamine – New type of antidepressant

- Anesthetic agent
- Fast-acting antidepressant
- o Single dose produces antidepressant effect within hours

- o Effects last 7-10 days
- o Effective in treatment-resistant depressed patients
- o Drug of abuse – hallucinogenic

This is great news!

We cannot use it yet, but researchers are working hard to determine how ketamine works with depression

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Thank you so much

[2016/06/18 09:31] Carolyn Carillon: QUESTION: Dr. Duric, will Virtual Ability be posting your slides, or will you make them available on SlideShare?

[2016/06/18 09:31] Carolyn Carillon: VD: We haven't done it yet but we can definitely set that up

[2016/06/18 09:31] LV (lorivonne.lustre): VD: We can definitely share the slides

[2016/06/18 09:32] Carolyn Carillon: VD: I have additional materials, too

[2016/06/18 09:31] LV (lorivonne.lustre): VD: I will try to answer some quick questions

Here is my contact information

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[2016/06/18 09:31] Sister (sister.abeyante): QUESTION: I am wondering about whether you have compared across cultures? Are there cultural differences?

[2016/06/18 09:32] Carolyn Carillon: VD: That's a good question

I'm not aware

if there are significant cultural differences

they might be more specific for a certain disease

rather than in general

[2016/06/18 09:32] iSkye Silverweb: The board in front of the podium has handouts from some of today's presenters

[2016/06/18 09:32] Gentle Heron: QUESTION: Dr Duric, you gave us a lot of information about negative effects of stress. But stress isn't all negative. There is eustress, or positive stress, that raises your attention, mental processes, and abilities. Is it possible for a person to change how they experience stress from distress to a more helpful form of stress that is motivational?

[2016/06/18 09:33] Carolyn Carillon: VD: I would say yes with practice or coaching

certainly in terms of performance

there's a stress curve

on one end, if you have too little stress, your performance won't be good

it's best when your stress is optimal

you need some stress to do well

some of the butterflies you feel in your stomach

that's good stuff

it keeps you focused

it has to be at the optimum level

at the other end of the curve is too much stress

that's negative

if you can train yourself to keep yourself at the optimal range

that can affect your performance

I hope that answers the question

[2016/06/18 09:32] Doc Neuro Cyants (ecoli.gynoid): QUESTION: What is your opinion concerning the use of neurofeedback for the treatment of anxiety and or depression?

[2016/06/18 09:35] Carolyn Carillon: VD: it can be useful

there are studies where people are trained to use biofeedback

where people see the image of their brain in real time

and people can learn to control certain areas of their brain

the ACC part of the brain

people can control the levels of pain, for example

that's one example I've seen

other things are a bit more clinical

some people with more clinical experience might be able to answer that better

but neurofeedback can be useful

[2016/06/18 09:36] Jadyn Firehawk: QUESTION: may i ask, what can you say about episodes of decompensation in PTSD and/or bipolar disorder in response to stress? i tend to think of it as a "rain barrel" sometimes, with a "spillover" threshold, is that in any way an appropriate analogy?

[2016/06/18 09:37] Carolyn Carillon: VD: That's outside my area of expertise I don't know

[2016/06/18 09:37] Jadyn Firehawk: tyvm

[2016/06/18 09:37] Sister (sister.abeyante): QUESTION: Given the clear links between chronic pain and mental illness, I am wondering if/when primary care providers will begin to treat so as to prevent the significant impact of depression, etc. on quality of life? You mentioned that currently, this is not part of the initial treatment protocol. What has to happen to make it so?

[2016/06/18 09:38] Carolyn Carillon: VD: That's a great question  
As far as I know, the mental health aspects do not start to be treated until they are diagnosed

at that point, you're playing a catch up game  
and you're dealing with severe disorders  
in my opinion, starting to address emotional aspects of chronic pain  
to minimize the mental health aspects of these disorders  
they should be considered in the initial treatment regimen  
when I was a grad student  
a lot of people were just looking at us  
when we started looking at the brain  
but with the development of MRIs etc  
we're starting to learn more about how pain affects the brain  
more research is being done  
that's good news  
it's a movement in the right direction  
it takes a while before science catches up but one day we'll get there

[2016/06/18 09:40] Gentle Heron: last question from Shyla: QUESTION: I have many doctors who do not treat chronic pain as having special significance with regard to mental or physical implications. How can a person with severe chronic pain effectively advocate for 'special care consideration' with their health care providers?

[2016/06/18 09:41] Carolyn Carillon: VD: you can show him some of the statistics  
maybe they're not aware of it  
it goes well with what I was talking about  
if you ask the average physician  
they may say "you're not depressed now so why should I treat you for it"  
they're treating the symptoms  
not looking at the body as a machine that has to maintain homeostasis  
so everything is in balance  
There's a lot of literature out there  
the emotional aspects of pain are starting to become more prominent  
10 or 15 years ago nobody was talking about that  
but now we're looking at the connection between the gut & brain  
when we presented the stress model  
one of my colleagues said they wanted to see how pain is connected to the gut microbiota  
things are moving forward  
but not sure how long it will take before we get some translation into the clinic  
but i'm not a clinician

[2016/06/18 09:44] Douglas Andrews (douglas.rishmal): What's interesting is ketamine being considered beneficial when it has been considered something abused for many years..  
(especially in the 'rave'/dance music community.)

[2016/06/18 09:43] Gentle Heron: Thank you Dr. Duric. We need to let Ms. Arzt have time to set up. I'm sure our audience could keep you responding for much more time. You've given us a lot to think about. Perhaps we can invite you back again to share more with us.

[2016/06/18 09:43] Shyla (krijon): thank you very much !

[2016/06/18 09:43] Anya (anya.ibor): Thank you, this was excellent

[2016/06/18 09:43] Sister (sister.abeyante): Thanks- very good presentation.

[2016/06/18 09:43] MatildaMoontree: Thank you Dr. Duric.

[2016/06/18 09:44] iSkye Silverweb: Yes!

[2016/06/18 09:44] Jady Firehawk: thank you so much! this is INCREDIBLY helpful

[2016/06/18 09:44] Ruby Vandyke: yes, thank you for all the great information!

[2016/06/18 09:44] Carolyn Carillon: VD: thank you very much for inviting me I'll stay in touch!

My contact info is there

I'm not a clinician

but if you have questions about how things work in the body, I can help with that

[2016/06/18 09:45] LV (lorivonne.lustre): <transcription ends>