



ECNP

*neuroscience
applied*

**ECNP SEMINAR IN
NEUROPSYCHOPHARMACOLOGY**



20-22/05/2016 VIHULA MANOR, ESTONIA

Introduction

ECNP is an independent, non-governmental, scientific association dedicated to the science and treatment of disorders of the brain. Founded in 1987, its goal is to bring together scientists and clinicians to facilitate information-sharing and spur new discoveries.

The objective of ECNP is to serve the public good by stimulating high-quality experimental and clinical research and education in applied and translational neuroscience. It seeks to do this by:

- Co-ordinating and promoting scientific activities and consistently high-quality standards between countries in Europe.
- Bringing together all those involved in or interested in the scientific study of applied and translational neuroscience by arranging scientific meetings, seminars, and study groups.
- Providing guidance and information to the public on matters relevant to the field.
- Providing a format for the co-ordination and for development of common standards in Europe.

To fulfil this aim ECNP organises, amongst others, yearly the ECNP Congress that comprises of 6 plenary lectures, 28 symposia and 7 educational update sessions. The annual meeting attracts around 6,000 psychiatrists, neuroscientists, neurologists and psychologists from around the world and is considered to be the largest congress on applied and translational neuroscience.

ECNP organises seminars, as the one you have been invited to participate, in areas of Europe where there are less opportunities for psychiatrists to participate in international meetings. Interaction is the keyword at these meetings and they have proved very successful both for the participants and for the experts. During the seminar we discuss clinical and research issues that the local organisers feel that are needed to be covered and using these topics as a model for teaching how to ask a research question and how to plan an effective study. Leading ECNP experts that are also talented speakers will facilitate mutual discussion in small groups allowing you to present your abstract and get feedback from your colleagues and local mentors.

So far, ECNP has organised this meeting in Poland, Estonia, Turkey, Bulgaria, Slovak Republic, Hungary, Czech Republic, Moldova, Romania, Greece, Russia, Latvia and recently in Macedonia, Armenia, Georgia, Serbia and Lithuania. In some countries we have organised it more than once.

ECNP also supports on an annual basis participation of 100 junior scientists and researchers in an intensive three-day Workshop in Nice. Other educational activities of ECNP include the journal *European Neuropsychopharmacology* that promotes scientific knowledge along with publishing consensus statements. In addition, since 2009 ECNP organises a summer school of neuropsychopharmacology in Oxford, since 2012 a school of child and adolescent neuropsychopharmacology in Venice

and since 2013 a school of old age neuropsychopharmacology in Venice. This autumn a Workshop on Clinical Research Methods will take place in Barcelona, Spain.

ECNP will also continue the successful pilot of the ECNP Research Internships. A selected group of senior researchers will offer a short two week exploratory experience in their institutions. The hosting scientist is encouraged to establish a long term relationships with the applicant and teach a basic translational research method that the participant can use at home when he/she returns.

Please see the ECNP website (www.ecnp.eu) where you can find information about all the above initiatives and additional information and look for the activity that fits you.

I hope you have a fruitful and inspiring meeting in Estonia!

Gil Zalsman

Chair ECNP Educational Committee

Programme
ECNP Seminar in Neuropsychopharmacology
20-22 May 2016, Vihula, Estonia

FRIDAY 20 MAY 2016

Arrival of participants and experts

19.00 Welcome and dinner at the Hotel

SATURDAY 21 May 2016

- 09.00 – 09.15 What is ECNP?
 Introductions to the programme
 Speaker: Avraham Avital, Israel (seminar leader)
- 09.15 – 10.00 Animal model for social cooperation: implications in PTSD as a model for research plan and design
 Speaker: Avraham Avital, Israel
- 10.00 – 10.45 Evaluation and management of suicidal patients
 Speaker: Vladimir Carli, Sweden
- 10.45 – 11.30 Coffee break
- 11.30 – 12.15 The intriguing relationship between psychoactive substances and suicide: From the clinical world to basic science
 Speaker: Gal Shoval, Israel
- 12.15 – 12.30 How to give a talk
 Speaker: Avraham Avital, Israel
- 12.30 – 13.30 Lunch

Presentation participants in 3 groups in 3 parallel workshops			
Round 1 13.30 – 15.00	Gal Shoval, Israel <i>and</i> Aleksander Zarkovski Group 1	Avraham Avital <i>and</i> Eduard Maron Group 2	Vladimir Carli <i>and</i> Jaanus Harro Group 3

15.00 – 15.15 Break

15.15 – 15.45 Panel discussion: How to prepare a clinical research project and how to publish it

Chair: Avraham Avital, Israel

Panel members: Gal Shoval, Israel
 Vladimir Carli, Sweden

16:00 – 21.00 Cultural event

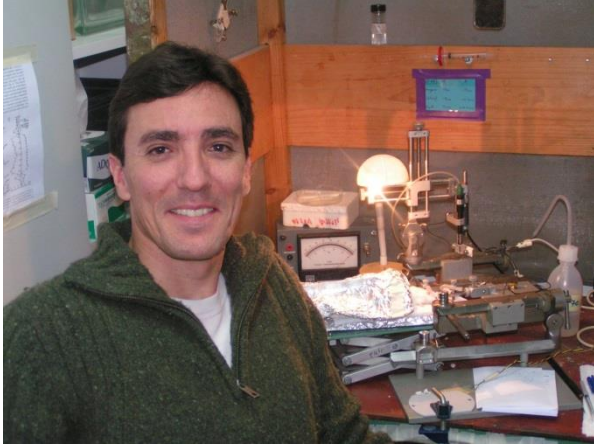
SUNDAY 22 May 2016

Presentations participants in 3 groups in 3 parallel workshops
(Experts rotate between the groups)

Presentations participants in 3 groups in 3 parallel workshops <i>(Experts rotate between the groups)</i>			
Round 2 08.30 – 10.00	Gal Shoval, Israel <i>and</i> Aleksander Zarkovski Group 2	Avraham Avital <i>and</i> Eduard Maron Group 3	Vladimir Carli <i>and</i> Jaanus Harro Group 1
10.00 – 10.30 Coffee Break			
Round 3 10.30 – 12.00	Gal Shoval, Israel <i>and</i> Aleksander Zarkovski Group 3	Avraham Avital <i>and</i> Eduard Maron Group 1	Vladimir Carli <i>and</i> Jaanus Harro Group 2
12.00 – 14.00 Lunch and preparation for plenary session			
Plenary 14.00 – 15.00	14.00 – 14.20	Group 1 Presentation	
	14.20 – 14.40	Group 2 Presentation	
	14.40 – 15.00	Group 3 Presentation	

15.00 – 15.30 Break and faculty selection of awards winners. Completion of feedback forms

15.30 – 16.00 Awards ceremony, concluding remark and thanks
Avraham Avital and Eduard Maron



Avi (Avraham) Avital is assistant professor in the Faculty of Medicine, the Technion - Israel Institute of Technology, and Emek Medical Center. As a board member The Israeli Society for Biological Psychiatry (ISBP), Avi is also the head of the young basic science leadership program, operating as part of the ISBP activities.

Avi serves as a member of the ECNP education committee.

In his behavioural Neuroscience Lab, they study the effects of life circumstances on emotional and cognitive processes. Specifically, the research is focused on attention processes and social cooperation. On the translational aspect, the lab studies Schizophrenia and PTSD in animal models and clinical researches. Both basic and clinical studies are nurturing and being nurtured by each other. The entire research in the lab is involving technological equipment including software and hardware that are custom-made.



Gal Shoval, M.D. is the director of the child & adolescent ER unit and the acting director of the adolescent day unit in Geha Mental Health Center, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Israel. Dr. Shoval's research interest focus on the link between suicidality, psychoactive substances and mood disorders among the young, using pharmaco-epidemiologic and animal model methodologies. Dr. Shoval served as a member of the National Treatment and Rehabilitation Committee under the Israeli National Anti-drug Agency and he is an active board member of the Israeli Society of Biological Psychiatry.



Dr. Vladimir Carli, MD, PhD, is Senior Lecturer in Prevention of Suicide and Mental Ill-Health at the National Centre for Suicide Research and Prevention (NASP), at Karolinska Institutet (KI). He is project leader of the project Suicide Prevention through Internet and Media-based Suicide Prevention (SUPREME), funded by the European Agency for Health and Consumers (EAHC), Assistant Project Leader of the 7th Framework Programme EU funded projects Saving and Empowering Young Lives in Europe (SEYLE) and Working in Europe to Stop Truancy Among Youth (WE-STAY).

VC is Co-Director of the WHO Collaborating Centre for Research, Training and Methods Development in Suicide Prevention. He collaborated with the WHO in the development of the section on Suicide of the mhGAP intervention guide, and is co-chair of the workgroup on “Risk Factors and Evidence Based Interventions” that developed the corresponding section of the WHO World Report on Suicide (2014). VC is coauthor of more than 80 scientific publications on International, ISI journals. He regularly teaches about mental health promotion and suicide prevention to undergraduate, graduate and post-graduate students and supervises PhD students.

VC is Chair of the Suicidology Section of the World Psychiatric Association (WPA) and co-Chair of the Network on Suicide Prevention of the European College of Neuropsychopharmacology (ECNP).

VC’s current main areas of interest are in the field of e-delivery of suicide preventive interventions, development and evaluation of interventions for young people, development of collaborative online tools for researchers in suicidology, development of statistical methods for the evaluation of suicide risk.

Avraham Avital

Animal model for social cooperation: implications in PTSD as a model for research plan and design

Social cooperation is defined as a joint action for mutual benefit that depends on the individual and the counterparts' behaviors. To gain valid evidence for social cooperation behavior in rodents, in our maze the partners achieve equal rewards in a fully automated non-conditioned apparatus. In a series of experiments we depicted three major findings: (i) During 18 days of social cooperation learning, the rats showed a progressive learning curve as well as latent social learning; (ii) Examining the perceptual communication between the cooperating partners, we found a correlation between the available perceptual modalities and the social cooperation performance; and (iii) Investigating contextual learning as a competing process to the social cooperation, we found that additional contextual cues impaired the social cooperation performance.

In conclusion, our automated cooperation maze is designed to further our understanding of social cooperation under normal conditions, such as decision-making. In addition, a variety of neuropsychiatric disorders are characterized by disruptions in social behavior, including depression, autism spectrum disorders, and PTSD. Thus, on the pathological end, our automated maze can contribute significantly to the investigation of a wide range of social cooperation impairments in a rodent model and the effects of suggested treatments.



Animal model for social cooperation: implications in PTSD as a model for research plan and design

Avraham (Avi) Avital, Ph.D
*Behavioral Neuroscience lab,
The Bruce Rappaport Faculty of Medicine, Technion- Israel Institute of Technology*

Introduction

Methylphenidate and Desipramine Combined Treatment Improves PTSD Symptomatology in a Rat Model

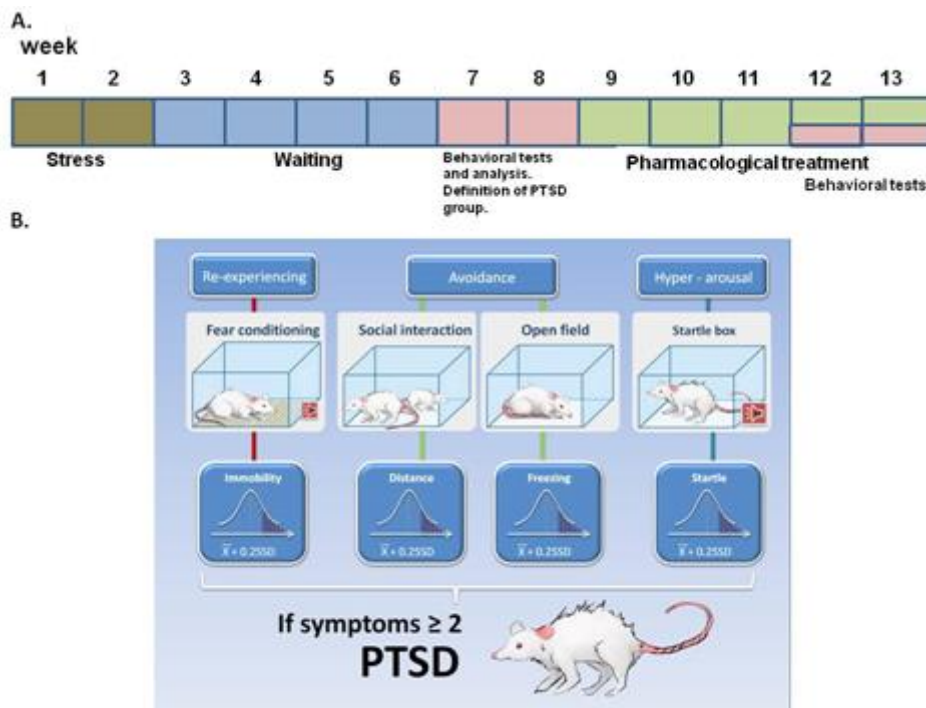
The characteristic symptoms of post-traumatic stress disorder (PTSD) include: re-experiencing, avoidance and hyper-arousal.

Nowadays, the common treatment for PTSD includes various antidepressants. However, these treatments focus on the anxiety, depression, flattened affect or detachment symptoms and less on attention problems.



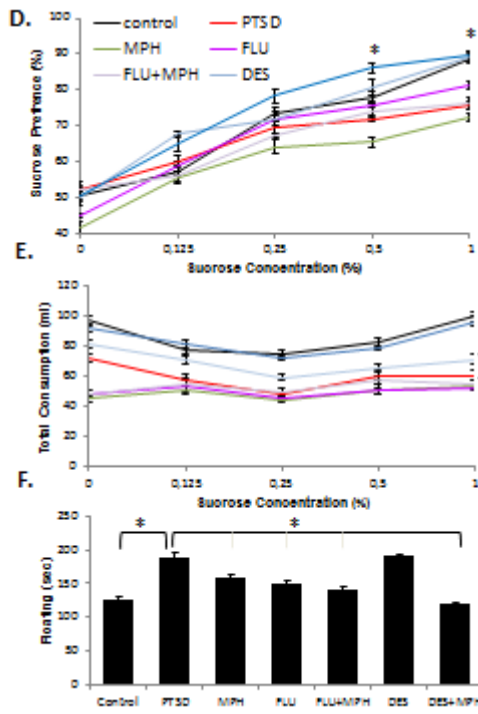
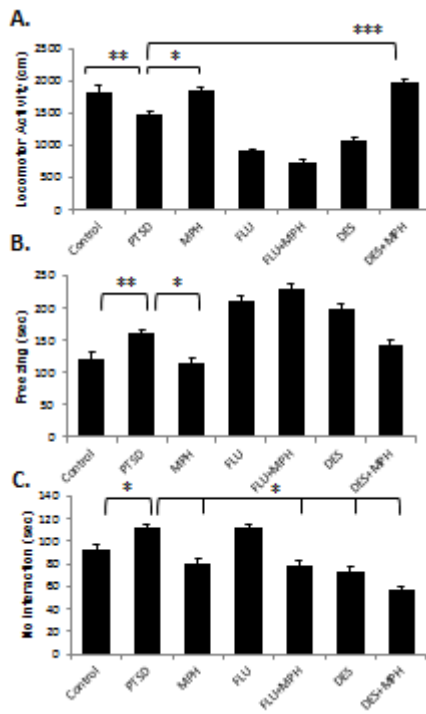
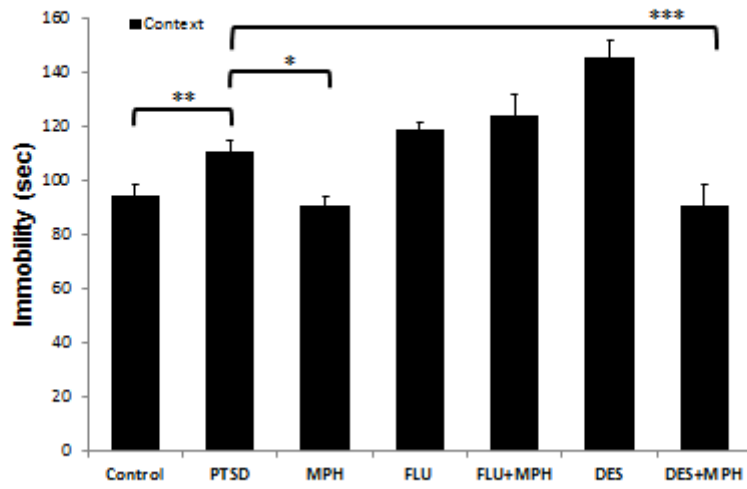
To determine whether, in addition to the common antidepressants, Methylphenidate (Ritalin) treatment will affect PTSD core symptoms.

Translational Psychiatry, 2014



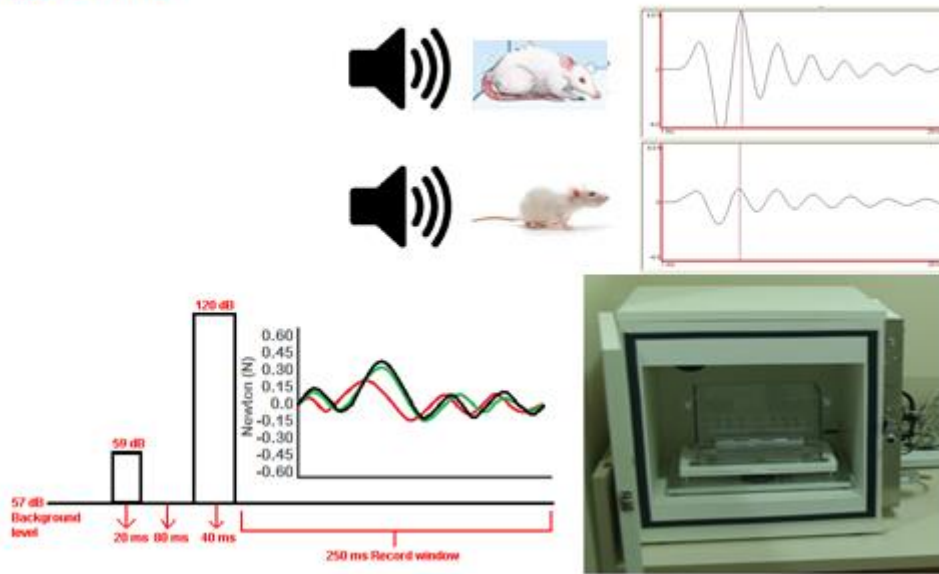
Results

Re-experiencing



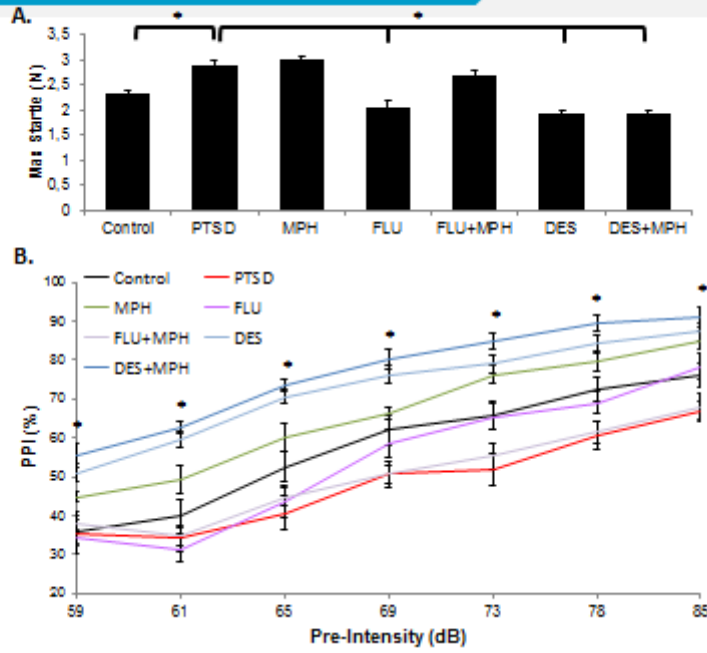
Methods

hyper-arousal



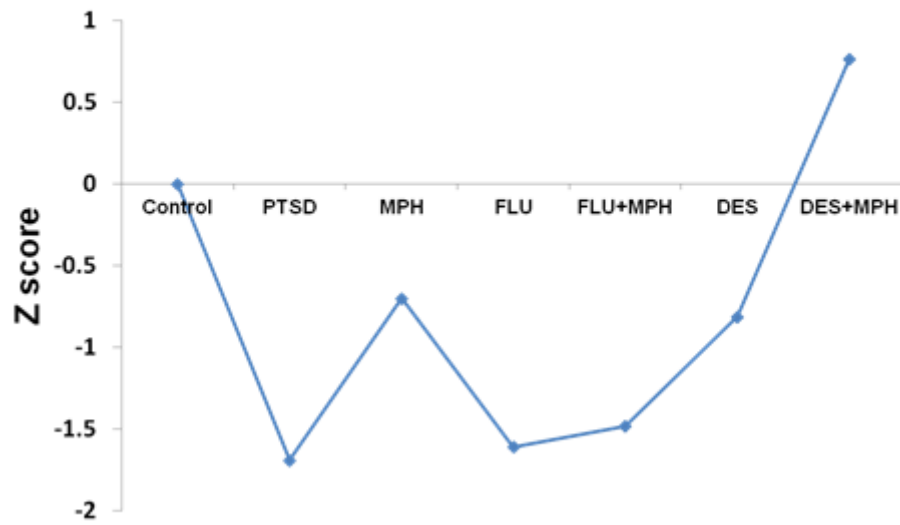
Results

hyper-arousal

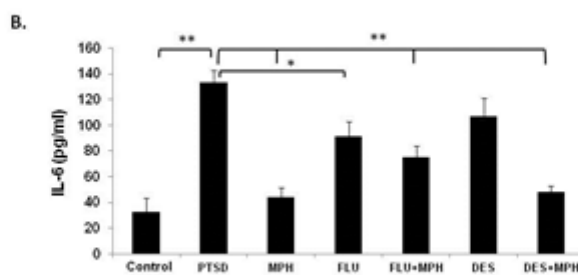
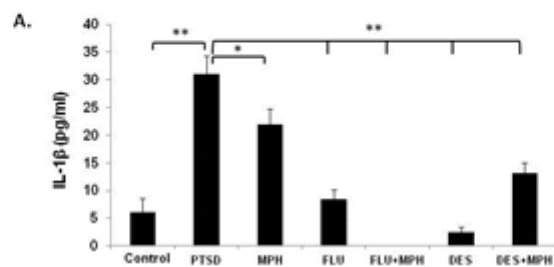


Results

Aim 2



Results



Conclusions

Considering the versatile emotional and cognitive symptoms of PTSD, our results suggest a new duo-treatment for PTSD comprised of antidepressant (desipramine) and psycho-stimulant (methylphenidate) that partially share norepinephrine-reuptake-inhibition mechanism.

PTSD as well as many other diseases/disorders accompanied by poor social abilities.

One answer leads to a new question



Introduction:

- Social cooperation underlies coordination toward a shared goal \ reward.



- Social cooperation is considered to be a trait shared by cognitively advanced organisms.

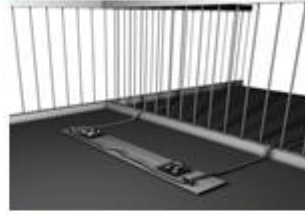


Exp. controlled environment

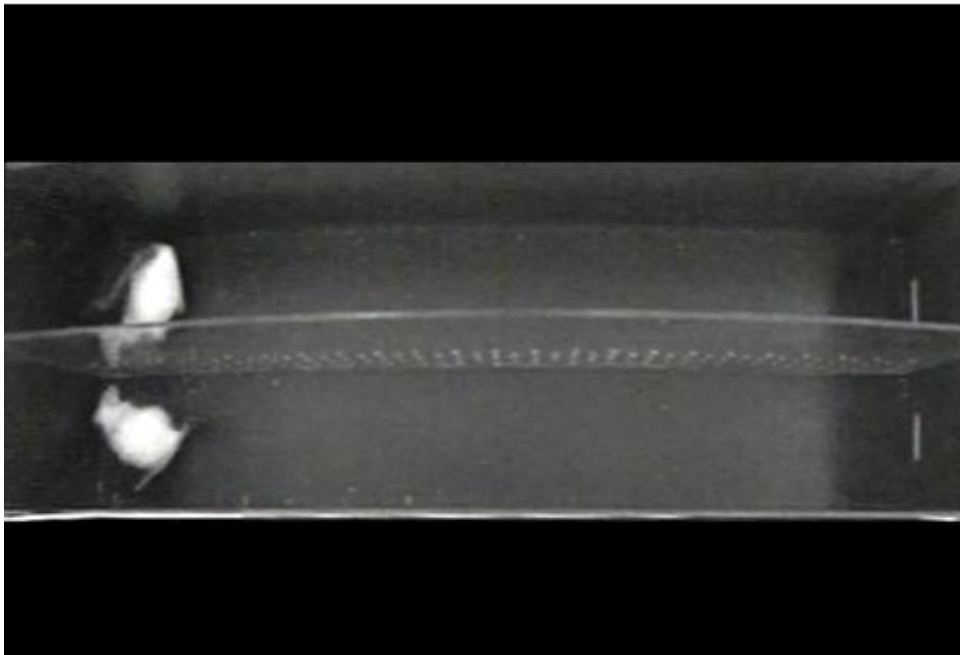


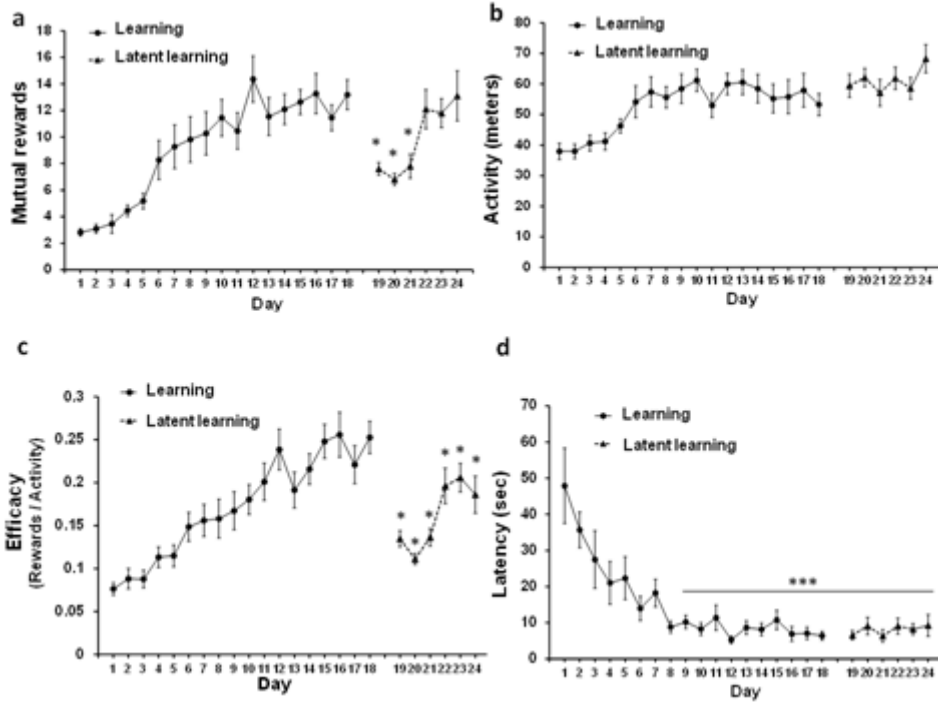
Ploshnik et al., 2011 (PNAS)

Pulling one end resulted in failure because the rope came unthreaded

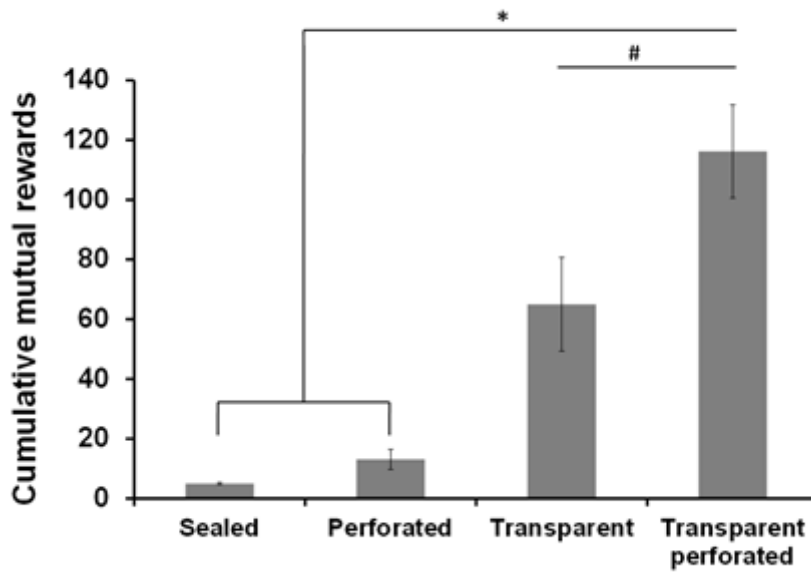


Hare et al., 2007 (Current Biology)



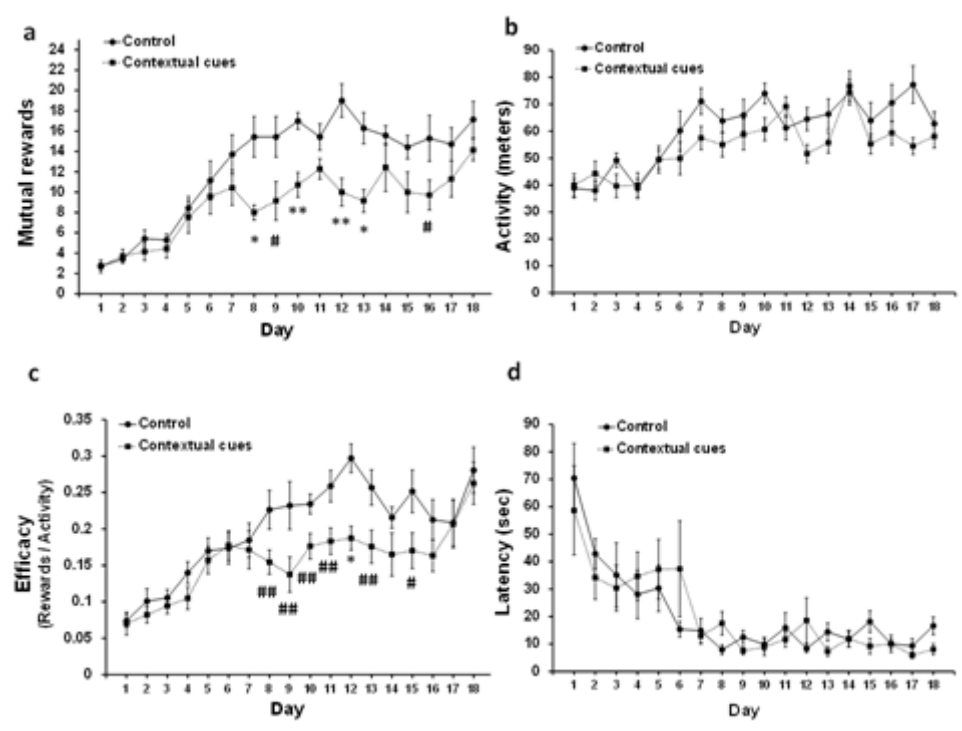


Sensory modalities

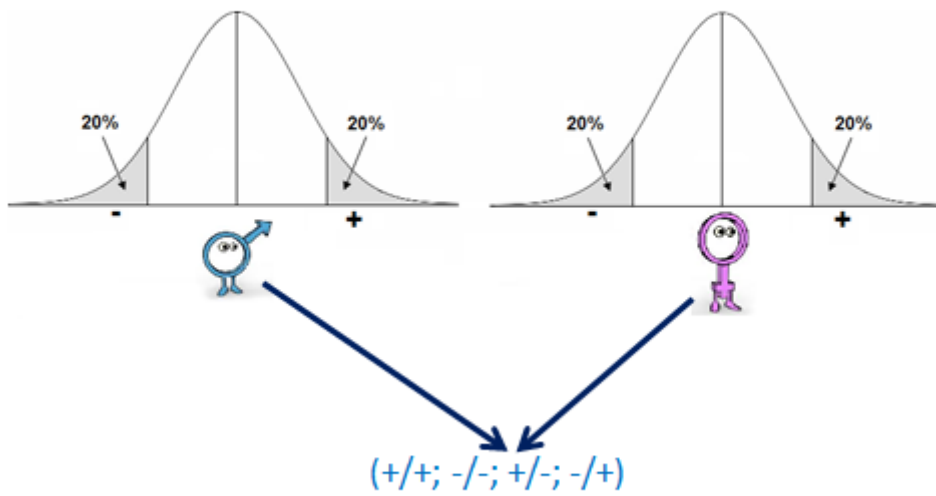


* = P < 0.0001; # = P < 0.011

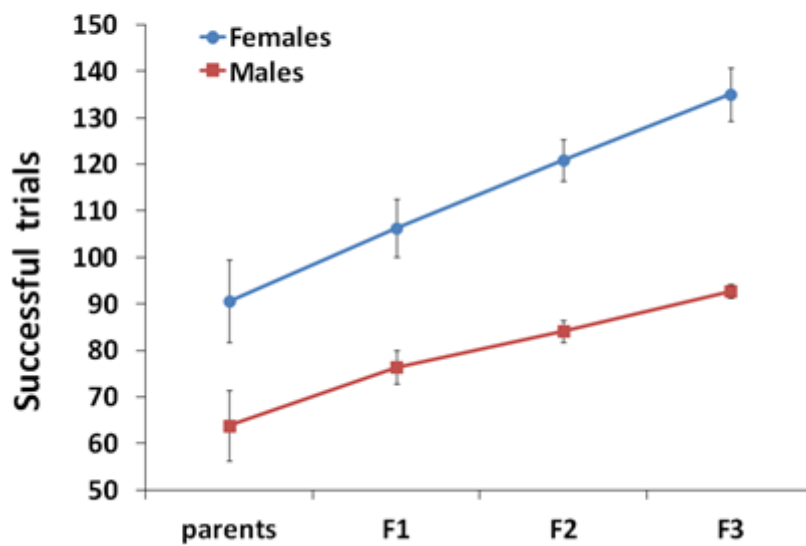
Attentional competition: Contextual versus Social



Counterbalanced breeding



Trans-generational effect



Conclusions

Our suggested cooperation maze is designated toward wide range of rodent models characterizing behaviors missing social cooperation and communication such as autism spectrum disorders , Down syndrome, Prader-Willi syndrome and last but not least, the neural basis of social cooperation.

Acknowledgments

Students :

Talya Dolev



Yael Hazan



Inon Maoz



Behavioral Neuroscience Lab's staff:



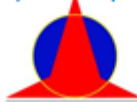
Dr. Shlomit Aga-Mizrachi



Mr. Salman Zubedat

This study is partially supported by:
Israel's MOD Directorate for

Defense Research &
Development (DDR&D)



US-Army Research Office
(ARO)



Gal Shoval

**The Intriguing Relationship between Psychoactive Substances and Suicide:
From the clinical world to basic science**

The relationship between suicidal behavior and the use of psychoactive substances has been the focus of past and current basic and clinical research attention. Despite that, substantial gaps remain. Whereas robust associations were established, causality is still not clear, and it is currently unknown how to approach this link clinically, for example – for the purpose of preventing suicide and non-suicidal-self injury (NSSI). The lecture describes comprehensively the existent literature, the major questions at stake and tease the audience to raise novel lines of research as to how new pharmacological strategies can be developed. Recent research by the speaker and others would be presented to demonstrate the various research possibilities ahead of us. Major "hot" topics such as alcohol and medical marijuana would be also discussed critically with potential clinical beneficiary implications vs. hazards and complications.

Vladimir Carli

Evaluation and management of suicidal patients

A large proportion of suicidal behaviour can be prevented, particularly in cases associated with mental disorders. We have now evidence that treatment of affective disorders, anxiety disorders, alcoholism, psychoactive substance misuse, schizophrenia and other psychosis can reduce suicide. However, before adequate treatment can be administered, a careful diagnostics procedure and evaluation of suicide risk is a prerequisite. Systematic clinical assessment of suicide risk is one of the most difficult tasks in psychiatric practice.

Evaluation of suicidal risk involves assessment of suicidal intent, previous suicide attempts, underlying psychiatric disorders, the patients' personality, the social network, suicide in the family or among acquaintances as well as the patient's suicidal communication. Suicide risk assessment should take place on several levels and relate to the patient, the family and social network and also to the availability of treatment, rehabilitation and prevention resources in the community.

Existing evidence supports the efficacy of pharmacological treatment and cognitive behavioural therapy (CBT) in preventing suicidal behaviour. Some other psychological treatments are promising, but the supporting evidence is currently insufficient. Studies show that antidepressant treatment decreases the risk for suicidality among depressed patients. However, the risk of suicidal behaviour in depressed patients treated with antidepressants exists during the first 10-14 days of treatment, which requires careful monitoring. Short-term supplementary medication with anxiolytics and hypnotics in the case of anxiety and insomnia is recommended. Treatment with antidepressants of children and adolescents should only be given under supervision of a specialist. Long-term treatment with lithium has been shown to be effective in preventing both suicide and attempted suicide in patients with unipolar and bipolar depression.

A multidisciplinary treatment team including psychiatrist and other professionals such as psychologist, social worker, and occupational therapist is always preferable, as integration of pharmacological, psychological and social rehabilitation is recommended especially for patients with chronic suicidality.

The issue of patient's safety is also of paramount importance. A secure home, public and hospital environment, without access to suicidal means is a necessary strategy in suicide prevention. Each treatment option, prescription of medication and discharge of the patient from hospital should be carefully evaluated against the involved risks.

Evaluation and Management of Suicidal Patients

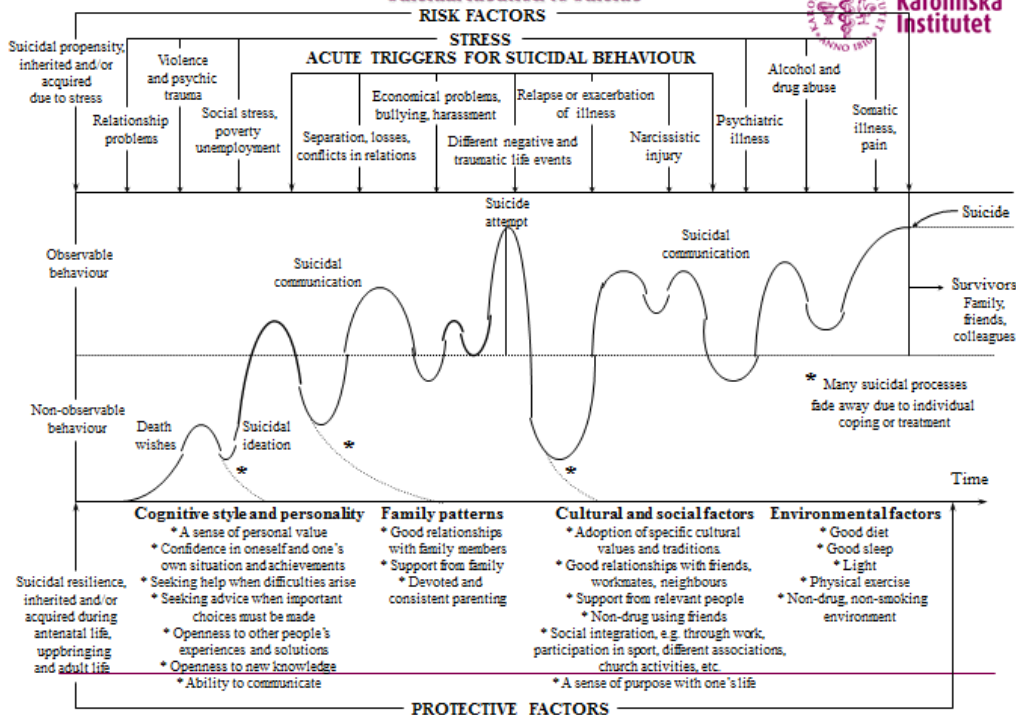
Vladimir Carli

*Senior Lecturer at the the National Centre for Prevention of Suicide and
Mental Ill-health (NASP), Karolinska Institutet, Stockholm, Sweden
Co-Director for the WHO Collaborating Centre for Research, Methods
Development and Training in Suicide Prevention*

Suicidal behaviour is the most common psychiatric emergency

- **Treatment of suicidal behaviour is complicated by a series of factors:**
- **Suicide is ultimately not predictable**
- **Aspecific risk factors**
- **No shared pharmacological therapeutic strategy available**
- **High environmental stress and anxiety**
- **Need of multi-disciplinary therapeutic interventions**

Stress-vulnerability model and development of the suicidal process from suicidal ideation to suicide



Clinical challenges

- To protect patients against:
 - Repetition of attempted suicide
 - Suicide
- To reduce the patients' profound feeling of hopelessness
- To reduce:
 - Anxiety
 - Aggressivity
 - Ambivalence

Psychiatric Disorders

- 70% of people who commit suicide suffer from affective disorders.
- Depression is also implicated in many suicides where the primary diagnosis is schizophrenia, alcoholism or personality disorder.
- Psychotic features in depression increase suicidal risk.
- Schizophrenics account for 10% of suicides.
- Alcohol or drug abuse is the primary diagnosis in 15-30% of suicides.
- Patients with personality disorders provide the most ambiguous situation to the clinician and are often unpredictable.

The suicidal patient-doctor relationship **BE AWARE**

- The suicidal patients transference
- The role assigned to the doctor often involves repetition of the patients old conflicts and responses to them (parents and previous caregivers)
- The doctor can be seen as a saviour or an enemy
- Patients may hide their needs

The doctor's countertransference **BE AWARE**

- Empathy, commitment, but also feelings of helplessness, hopelessness and ambivalence
- Ambivalence towards the suicidal patient may result in misjudging suicide risk due to the doctors perception of only some symptoms and behaviours.
- Sometimes passive or verbal expressions of aggressive feelings.

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Evaluation of Suicidal Ideation

- Privacy
- Evaluation of patient's abilities
- Assess spontaneous verbalization of suicidal ideation
- No fear to induce suicidal thoughts
- Patients are often relieved by speaking of their suicidal tendencies
- First step in establishing the therapeutic alliance
- Not only "how much" but also "why"
 - Hopelessness
 - Cognitive factors
 - Consistency of suicidal motivation

Hopelessness

- May attribute failures as own fault or perceive self as burden because of ineffectiveness
- Triggered by various stressors such as retirement, lay off or dismissal, disciplinary action; situations involving embarrassment or shame, illegal activity, sexual assault, misappropriation of funds, etc.
- Cognitive set that underlies depression/suicidality—maintaining suicidal belief system

SR Assessment and Formulation

- **Suicide Risk Assessment (SRA)**
 - Gathering information on risk factors, protective factors and warning signs
 - Exploring the patient's suicidal process
- **Suicide Risk Formulation (SRF)**
 - Extremely important and usually underestimated.
 - Assigns a level of risk to an individual patient
 - Very little research has been performed about how to produce a SRF out of a SRA, what are the criteria to assign levels of risk.

“The SRF is dependent on the data gathered with the SRA. The SRF assigns a level of suicide risk that is intended to inform decisions about triage, treatment, management and preventive interventions”

Admission versus Ambulatory care

- Physical damage
 - Therapeutic alliance
 - Severity of psychopathology
 - Suicidal ideation and suicidal risk
 - Social support
-

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Hospitalization of the Suicidal Patient

- **Advantages - Security**
 - Hospitalization accounts for the highest possible security
 - Is not possible to achieve complete security. In US, 5% of all deaths for completed suicide occur in inpatient units
 - In Sweden <30% of patients commit suicide within 28 days after discharge from the hospital care, approx 10% in or in the vicinity of the hospital and 50-60% having had contact with the health care services within a month
 - If there is one suicidal patient in the ward, all patients should be considered as “suicidal”
-

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Hospitalization of the Suicidal Patient

▪ Disadvantages

- Loss of freedom can trigger the surrender of adult independence and regression
 - Involuntary hospitalization may often break-down the therapeutic alliance
 - Treatment cost is higher
 - Removes the patient from his usual environment
-

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Crisis Intervention

→ Short-term interventions for patient's health

- Physical damage
- Safety precautions
- Provide emotional support
- Treat acute psychiatric symptoms (Anguish, anxiety, insomnia)

→ Replace patient's tunnel vision with a broader perspective

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Discharge

- Is the most critical phase for every patient. Risk of repetitions is highest after discharge and decreases with time.
- 24 hour help phone line
- Social support available for the patient should be always considered
- Follow up should be planned before discharge
- A “protected” discharge should be considered with admission to a day clinic a day center or a residential facility.

Medium / Long-term therapeutic interventions

- Plan for follow up
 - Biological treatment
 - Psychological treatment
 - Social support
-

Medium to Long-term Treatment of Suicidal Behavior

TREATMENT OF THE UNDERLYING PSYCHIATRIC DISORDER

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Treatment of suicidal people with antidepressants Risks/Benefits

- Antidepressants in:
 - *Young people below age of 24 years*
(risk in some)
 - *Older persons above 65 years (benefit)*
- High-risk among
 - *Non-responders*
 - *During the first 10-14 days of treatment*
- Comorbid anxiety
- Insomnia
- Psychotic features

Barbui et al. CMAJ. 2009
Hazel. Clinical Evidence. 2008

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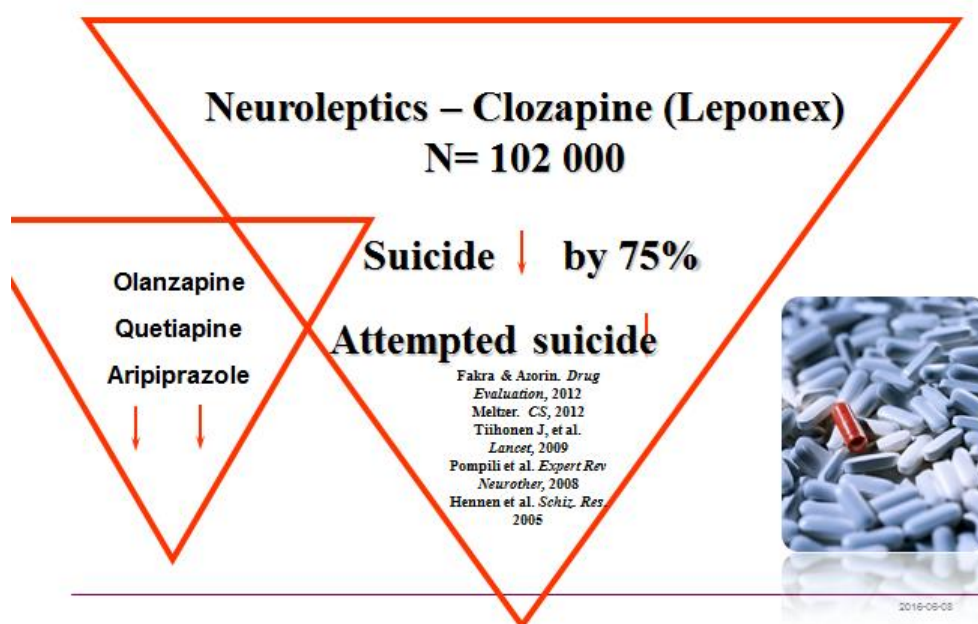
Treatment with Lithium

	<u>Outcome with lithium</u>	<u>Outcome without lithium</u>
Suicides		
Rate	0.167	0.793
(95% CI)	(0.109-0.224)	(0.592-0.995)
Subjects	14,308	1,370
Attempts		
Rate	0.407	4.021
(95% CI)	(0.154-0.660)	(2.040-6.003)
Subjects	898	651
All acts		
Rate	0.197	2.570
(95% CI)	(0.128-0.266)	(1.751-3.389)
Subjects	15,157	1,998

Baldessarini et al. *Annals of The New York Academy of Sciences*, 2006

2016-06-08 18

Treatment of schizophrenia



2016-06-08 20

Psychological treatments of suicidal behaviours

- **Good Evidence for:**
- Cognitive Therapy
- Cognitive Behavioural Therapy
- **DBT: Dialectical behaviour therapy for borderline personality disorder**

Shearin EN, Linnehan MM,
*Dialectal behaviour therapy for
borderline personality disorder:
theoretical and empirical foundations.*
Acta Psychiatr Scand 1994;89 (Suppl. 379):61-68





Akbar Zeb

Institute of Biomedicine and Translational Medicine, Department of Pharmacology, University of Tartu

Oxidative stress has been implicated in the pathogenesis of Parkinson's disease. To ameliorate oxidative stress, cells have evolved numerous protective mechanisms. One key protective mechanism is mediated by nuclear factor-erythroid2-related factor (Nrf2). Upon activation, Nrf2 has been shown to upregulate a network of antioxidant proteins and enzymes that play an important role in cellular defence system (Solis et al, 2002; Petzer et al, 2003). In this study, we aimed to explore the links between Nrf2 pathway and mitophagy specifically PINK1/Parkin pathway. Our initial results revealed that Nrf2 or its inhibitor Keap1 functionally interact with PINK1 as well as Parkin.

Katrin Orav

Private clinic, Vaimne Tervis OÜ, Tallinn

57 years old female Outpatient treatment in my company from 30.06.2014, about 30 outpatient sessions and 6 hospitalizations in Psychiatry due the relapses and dependence from analgetics and benzodiazepines. 2 hospitalization in Neurology. Disability 80%, referral to rehabilitation services. History of meningitis, facial nerve damage, gain weight 20kg. Previous outpatient treatment in the North Estonian Regional Hospital Psychiatric Clinic. ICD-10: F45.0 Somatoform disorder F13.22 Dependence on sedatives, currently controlled by treatment F33.10 - Recurrent depressive disorder, moderate episode without somatic symptoms G44.8 - Other specified headache syndromes, drug-induced headache (diagnosed in 26.11.2015) I44.1 - Atrioventricular and left bundle branch block, second degree atrioventricular block. 19.07.2015 Patient hospitalized for installing a pacemaker to second degree AV blockade (Mobitz II, 2: 1) E78.0 Pure hypercholesterolemia Z95.0 Over 2 weeks outpatient visits, psychotherapy has not started due to lack of trust, recognition and motivation. Ambulance calls and emergency room visits, fatal medical complications.

Aleksandr Bregin

Centre for Excellence in Translational Medicine, University of Tartu

HYPERSENSITIVITY TO BENZODIAZEPINES AND ALCOHOL IN LSAMP-DEFICIENT MICE

Limbic system-associated membrane protein-deficient (Lsmp^{-/-}) mice have been shown to exhibit less stressed behavior in novel environments, modified locomotive, fear-related, learning and social behaviors. The aim of this study is to determine whether the effects of common benzodiazepines (diazepam and alprazolam) and alcohol alter anxiety-triggered behavior in the studied mouse line compared to the wild-type. Our results show significant differences between Lsmp^{-/-} and wild-type mice in different behavioral assays. Due to the difference in the degree of hypersensitivity the two studied benzodiazepines, we intend to further study the changes in the GABAergic system of the Lsmp^{-/-} mice.

Jane Narvik

Centre for Excellence in Translational Medicine, University of Tartu

Schizophrenia is chronic disease that suppress cognitive functions. One of the first symptoms is psychosis. Our unpublished clinical data showed that during first psychotic episode there is a remarkable EGF protein elevation in blood. After pharmacological treatment with antipsychotics it normalized. Our interest is why and how EGF is related with the beginning and evolving of psychosis.

Katrin Kaarma

North Estonian Regional Hospital, Psychiatry Clinic

Case

The aim of this presentation is to discuss the possible choices of psychotropic medicine for the patient with familial hypercholesterolemia presenting mild cognitive disorganization, social isolation and mood decrease. We are in the process of differential diagnosis currently. First hypothesis are: depression with psychosis, psychosis prodrome or depression with pre-existing pervasive traits.

According to patient's mother's description, his behaviour has changed during last 2-3 years. He graduated 9 classes in his school and then attended the gymnasium in another school with technical direction. He didn't cope there, missed the classes and finally stayed at home from January 2015. During these years, in 2013, 2014 he contacted medical service several times and had multiple bodily complaints as well as complaints about dizziness, tiredness, anxiety and mood decrease. These were diagnosed as symptoms connected with emotional state. From family history: his father had heart attack in 2011, brain infarctus in 2013 and died after second heart attack in July 2015

Previously he had been in psychiatric hospital in June 2015. His condition was diagnosed as adjustment disorder with depressive anxious reaction. Mirtazapine and later quetiapine were ordained. Patient soon discontinued them. Risperidon was also prescribed but patient said he felt awful and suicidal thoughts appeared, so he used it only for few days.

Currently referred by ambulatory psychiatrist with probable psychosis prodrome. Blood tests were otherwise normal except cholesterol - In 02.2016 -Chol 6,7; LDL 5,22; HDL0,97. In comparison previous tests: in 06.2015 Chol 8,2; LDL 6,5; HDL1,42. And in 2009 Chol 9,37;LDL 7,46; HDL 1,36. Aripiprazol was chosen for treatment, because of low metabolic effect. It is even found to lower the lipid level raised by olanzapine and clozapine (discussion about AP effect on cholesterol). Patient didn't agree to take it. As patient had also low mood and sleeping problems, I offered agomelatine. I could find some information about melatonin metabolic neutrality in the literature. I was assuming that agomelatine will act similarly. (Discussion about AD effect on cholesterol) But this is not the same with SSRI-s, for example there is a study showing the effect of sertraline and paroxetine use on LDL elevation. Main topic to discuss. What are the suitable AP-s and or AD-s for treating psychosis prodrome in patient with hypercholesterolemia?

Karola Peebo

The North Estonia Medical Centre, Psychiatry Clinic

Case report

A 15 year old girl was admitted to neurology department with sudden onset monoplegia of the left leg. She had woken up from a nap and could not feel or move her leg. On neurological examination she demonstrated algesia and plegia of the left leg from the groin downward. With tests such as MRI and ENMG organic pathology was excluded. With information from the patient and her mother, it was clear that the patient had a very complicated family situation. She regained minimal function in her left leg with physiotherapy and psychotherapy. We diagnosed dissociative motor disorder.

Jekaterina Kress

The North Estonia Medical Centre, Psychiatry Clinic

46 year old women was admitted to Psychiatric Hospital for the 11 time due to episode of full-blown mania. Personal and patients were significantly disturbed by her increased activity. Resident of internal medicine realized, that patient had really blue lips and Astrup confirmed hypothesis of low saturation. Afterward many causes of hypoxemia were excepted. Despite of low saturation patient was continually manic and needed high doses of medication. Patient said, that lipstick always helped her to hide pallor of her lips. Nor she or her mother were worried because of it and they did not want further evaluation. For me, the cause of chronic hypoxemia and its effect on patient mental disease still remains unclear.

Tõnis Tasa

Estonian Genome Center, University of Tartu; Institute of Computer Science, University of Tartu

DosOpt: A web-based therapeutic drug monitoring tool for individualized Bayesian dose optimization

We present a web-based application for individualized dose adjustments in vancomycine treatment of neonates, DosOpt. It combines information from underlying pharmacokinetic model and provided data to patient-specific estimates using Bayesian methods. Derived individual drug response estimates are used in forecasting future treatment courses and in target-controlled dose optimization. We validated DosOpt using retrospective data from University of Tartu and Tallinn hospitals from 2010-2015. Increasing number of available concentration measurements from 0 to 3 decreased mean absolute prediction error from 61.2% to 22.8%. Systematic PK model underprediction bias was eliminated with 2 included patient data concentration measurements.

Natalia Lobanovskaya

University of Tartu, Institute of Biomedicine and Translational Medicine

Department of Pharmacology

Polysialylated neural cell adhesion molecule (PSA-NCAM) plays important roles in the regulation of the neuroplasticity. In our study, we investigated the roles of polysialylated neural cell adhesion molecule (PSA-NCAM), which abundantly expressed in the survival of the retinal ganglion cells (RGCs) after administration of glutamate receptor antagonist kainic acid. Administration of neuroaminidase an enzyme, which removes PSA residues from the surface of NCAM, enhanced the excitotoxic effects of KA on RGS. In knockout mice with constitutive deficiency of either polysialyltransferase ST8SialII or ST8SialIV genes, the levels of PSA-NCAM did not differ from those found in wild type mice. Our data demonstrated that PSA-NCAM supports the survival of injured RGCs in adulthood.

Jürgen Kütner

The North Estonia Medical Centre, Psychiatry Clinic

Patient: Male, 29 years old

The patient's first contact with a psychiatrist was in 2013, when he turned to the North Estonia Regional Hospital's Outpatient Clinic. His first symptoms included sleeping disturbances, mainly trouble getting to sleep, depressed mood and occasional periods of excessive anxiety. A diagnosis of F41.2 Mixed anxiety and depressive disorder (according to ICD-10) was made. The patient was then treated with agomelantin (Valdoxan) 25mg x1. 2 months later he was admitted to the Acute Psychiatric ward of the North Estonian Regional Hospital with a psychotic episode. The patient received antipsychotic treatment. Later, the patient has had recurrences of psychotic symptoms and has been admitted as an inpatient 4 times altogether. He has received several treatment options, has had problems with dystonias and compulsive behaviour, and as a whole is responding poorly to the treatment.

Lauri Keskaik

North Estonia Medical Centre, Emergency Medicine Centre

A 54-year-old woman was admitted to the emergency department because of increasing fatigue and behavioural disturbance. She had been diagnosed with schizoaffective disorder and high blood pressure. Physical examination showed mild hypothermia, GCS was estimated 14 (4+4+6), patient showed inadequate behaviour, neurological examination revealed no focal deficits. Further investigation revealed a normal CT scan, normal laboratory findings, except electrolyte derangement (P-K 2.4; P-Na 105). She was placed on the internal medicine ward. The patient was managed with infusion therapy for electrolyte correction. The next morning laboratory analyses revealed normal electrolyte panel, but physical examination showed altered neurological status.

Q: Possible causes of hyponatremia?

Q: Cause for the decline in neurological status?

Anne Lang

North Estonian Medical Centre, Child and Adolescent Psychiatry

14-year-old girl was hospitalized to child psychiatry department due to depressive thoughts, self-injuring behaviour and suspicion of psychotic disorder. During inpatient treatment patient presented delusions of persecution and grandiosity, imperative vocal hallucinations, feelings of depersonalization and derealization. In addition the patient was diagnosed with autism spectrum disorder. The patient was treated with olanzapine 10 mg which had a dramatic effect on psychotic symptoms. Soon the patient was rehospitalized due to persistent depressive thoughts and self-injuring behaviour. Citalopram 10 mg was added to olanzapine hoping to relieve depressive symptoms. During citalopram treatment patient started to have tachycardic episodes and citalopram was switched to fluoxetine 20 mg. During fluoxetine treatment patient started to have psychotic symptoms again and was as depressive as before rehospitalization. This case report illustrates the difficulties treating depressive patients with psychotic disorder.

Kati Külm

North Estonia Medical Centre, Psychiatry Clinic

22 year old male patient was hospitalized from military service with symptoms of apathy, irritability, occasional panic attacks, and sleep disturbances. According to medical history he had been visiting doctors from different fields since 2011. From 2011 to 2015 had been diagnosed with unspecified episode of depression, unspecified bradycardia, dyspepsia, headache and migraine with aura. He had received antidepressant treatment with Escitalopram, which turned out to slightly worsen previously existing symptoms. During current hospitalization he was diagnosed with acute polymorphic psychotic disorder without symptoms of schizophrenia and received treatment with antipsychotic Olanzapine, which turned out to be effective. The patient may have been having the prodromal symptoms of psychosis for years before current hospitalization. Detecting the early signs of psychosis can present a challenge to clinicians from all fields of medicine and significantly delay making a right diagnosis and receiving appropriate treatment.

Alexandra Buchelovskaya

Tartu University Hospital, Rheumatology

Systemic lupus erythematosus (SLE) and psychosis

Organic psychosis occurs in approximately 5% of patients with SLE, usually within the first two years after the onset of disease. It is a diagnosis of exclusion. The most challenging is to differentiate SLE psychosis from one induced by corticosteroid therapy. It has been observed, that auditory hallucinations are usually caused by steroid therapy, while visual and tactile disturbances are most frequently due to SLE. Glucocorticoid-induced neuropsychiatric disturbances generally resolve with discontinuation or lowered dose of glucocorticoids. Psychological symptoms are best treated with typical antipsychotic drugs (such as haloperidol). Psychosis due to (active) organic involvement by SLE

usually responds to steroids. Treatment should be initiated as soon as possible to prevent permanent damage. Prednisone (1 to 2 mg/kg per day) given for a few weeks in divided doses is usually sufficient. If no improvement is seen within two to three weeks, a trial of cytotoxic therapy (eg, pulse cyclophosphamide) is warranted.

Liina Pappa

Institute of Molecular and Cell Biology, Department of Biotechnology

Neural tube defects (NTDs) represent common (0.5-2 births in 1000 pregnancies) and severe congenital malformations that are caused by defects in neural tube closure during early embryonic development. In Estonia the NTD occurrence is - for yet unknown reasons - higher than in most other European countries. The study was carried out in collaboration with paediatricians at Tallinn Children's Hospital, where a cohort of multiplex families with patients with NTD diagnosis and sporadic patients was assembled, and the Estonian Biobank, University of Tartu. After assembling the cohort, samples of genomic DNA were extracted, followed by the CNV analysis with Illumina HumanOmni microarrays. During the microarray analysis in 4 trios, no possibly pathogenic de novo CNVs were detected, warranting further exome sequencing to be performed.

Triinu Keskpaik

North Estonian Medical Centre, Emergency Medicine

A 43-year-old male presented to the emergency department due to progression of deterioration. He had been admitted to the acute psychiatric department one day before diagnosed with acute psychosis. His medical history revealed alcohol abuse, high blood pressure, epileptic seizure with a head trauma three days before. Physical examination showed altered mental status (GCS 3), low blood pressure, tachycardia 146 beats per minute, tachypnea 36 breaths per minute, saturation 78% with room air and signs of dehydration. His core temperature was 41°C. Heart and lung sounds were normal.

Q: what is the cause of psychosis?

Q: what is the cause of patient deterioration?

Q: how to stabilize the patient?

Ilona Jäger

North Estonian Medical Centre, Emergency Medicine

A 78-year old male patient in the intensive care unit with a suicide attempt (knife injury to the neck). Previously no psychiatric history, his wife had died ca 1 year ago. During the previous months

relatives noticed that patient's behaviour changed, he started acting differently, did not sleep, had fears that someone tried to harm him (became psychotic).

Olga Dzyuba

The North Estonia Medical Centre, Psychiatry clinic

A male, 68 year old patient with previously diagnosed depressive disorder was admitted to psychiatric hospital because of worsening of depressive symptoms. He was diagnosed with recurrent depressive disorder (current episode severe with psychotic symptoms). Previously ordained pharmacological treatment had only partial effect, and in addition patient refused to eat. It was planned to perform electro-impulse therapy, but patient was discovered an abdominal aortic aneurysm in computer tomography. Dilemma of this clinical case: is there any risk of performing electro-impulsive treatment to a patient who has been diagnosed an abdominal aortic aneurysm?

Kaili Anier

Biomedicine and Translational Medicine, University of Tartu, Pharmacology

Accumulating data suggest that epigenetic modifications, such as DNA methylation (catalyzed by DNA methyltransferases, DNMTs) contribute to drug-induced short- and long-term changes in gene expression and may regulate mechanisms underlying brain reward and drug addiction. Recent discoveries suggest that ten-eleven translocation (TET1-3) enzymes participate in DNA demethylation process and might also play a role in drug addiction. In our study, we show that acute and repeated cocaine treatment in the induction and expression phase of sensitisation upregulated Dnmt and downregulated Tet transcripts mRNA levels in the nucleus accumbens (NAc) and cerebellum of mice and these changes tightly correlated with Dnmt and Tet mRNA levels in peripheral blood cells. Our data also showed that cocaine challenge increased DNMT activity levels in the NAc and peripheral blood cells, decreased TET hydroxylase activity levels and enhanced global DNA methylation levels in the NAc. In addition, bilateral intra-NAc injection of non-nucleoside inhibitor of DNMT RG108 diminishes the expression of cocaine-induced behavioural sensitisation after withdrawal and decreased DNMT activity levels in the NAc. These data indicate that cocaine treatment alters the balance between methylation and demethylation processes in the NAc and may affect the development of behavioural sensitisation.

Toomas Jagomäe

Institute of Biomedicine and Translational Medicine, Faculty of Medicine

Neural adhesion molecules of IgLON family consists of four proteins named LSAMP, NTM, OPCML, NEGR1. These molecules have been shown to facilitate neuronal migration, neurite outgrowth, axon guidance and synaptic development in formation of neuronal circuit. Imbalance in the expression of IgLON-s have been associated with prominent neuropsychiatric disorders. Three of the IgLON family

genes (LSAMP, OPCML, and NTM) have two alternative promoters and first exons (1a and 1b) which are active in different and often in complementary brain regions. Encoded proteins from alternative exons differ only in N-terminal signal sequences which are conserved in various phylogenetic branches. These observations suggest that selective pressure has acted to maintain this regulation of gene expression and that different functions exist for alternative N-terminal signal peptides. In the interest of understanding function of IgLON family signal peptides and interaction partners current thesis is proposed as two hypotheses: (1) alternative signal peptides designate localization and post-translational modifications; (2) IgLON family proteins act as co-receptors in central nervous system and interact with transmembrane receptor-molecules.

Kristi Krebs

Estonian Genome Center

A pharmacogenomics study using electronic health records and 2300 sequenced genomes

In the Estonian Biobank we have recently sequenced the genomes of 2300 participants. To identify genetic variants associated with adverse drug reactions (ADRs), we focused on 64 pharmacogenes known to influence various drug pathways. To examine the effect of such variants, we combined questionnaire data and electronic health records (EHRs) and compared the frequency of variant-dependent ADRs among subjects that had been prescribed drugs associated with the genes. For example, we found association between CYP2C9 alleles and ADRs among individuals taking Warfarin. Our results indicate that EHRs can serve as a powerful tool for identifying genetic variants associated with ADRs.

Anna Iofik

The North Estonia Medical Centre

Department of integrated treatment of first onset psychosis

As we all know, ADHD has been being diagnosed usually in early childhood. Therefore, its diagnosis within adult population currently represents a specific challenge. So, by the moment of the diagnosis establishment, the probability of comorbid diseases causes the difficulties in differential diagnosis, which complicates the resolution of symptoms varying from personality to mood disorders. Even if the former problem is resolved, the new challenge is treatment of adult patients with higher risk to acquire a cardio-vascular illness. The purpose of this report is to present one medical case, based on the medical history of 21-year old male patient diagnosed with ADHD. We focus on the choice of his medical treatment with the follow-up investigation invoked by the necessity to account for the increased risk of obtaining a cardio-vascular disease, based on his family medical record and personal complaints.

Viljar Veede

The North Estonia Medical Centre, Department of Psychiatry

22 year old male patient was hospitalized from military service with symptoms of apathy, irritability, occasional panic attacks, and sleep disturbances. According to medical history he had been visiting doctors from different fields since 2011. From 2011 to 2015 had been diagnosed with unspecified episode of depression, unspecified bradycardia, dyspepsia, headache and migraine with aura. He had received antidepressant treatment with Escitalopram, which turned out to slightly worsen previously existing symptoms. During current hospitalization he was diagnosed with acute polymorphic psychotic disorder without symptoms of schizophrenia and received treatment with antipsychotic Olanzapine, which turned out to be effective. The patient may have been having the prodromal symptoms of psychosis for years before current hospitalization. Detecting the early signs of psychosis can present a challenge to clinicians from all fields of medicine and significantly delay making a right diagnosis and receiving appropriate treatment.

Taavi Vanaveski

Institute of Biomedicine and Translational Medicine; Department of Physiology

The translational assessment of IgLON-KO mice lines as rodent models for schizophrenia research

The onset of schizophrenia in late adolescence or in early adulthood is believed to be a result of maladaptive synaptic pruning. Growing evidence suggests the importance of IgLONs as candidate genes in the susceptibility for schizophrenia. IgLONs have been shown to be involved with neurogenesis, neurite outgrowth, synapse formation and pruning, common functions shown to be altered in the brains of schizophrenic patients. Our aim was to characterize IgLONs in the mouse and human brain to estimate the validity of IgLON-KO mice lines as models in schizophrenia research.

Merle Mandel

University of Tartu, Department of Pharmacology

Neuronal growth is a complex and high energy demanding processes, where regulation of mitochondrial activity is therefore particularly important. However, precise mechanism how cellular energy generation is linked with physiological demand during neuronal development, remain unclear. Previous studies have shown that PPAR- γ co-activator 1 α (PGC-1 α) is a master regulator of mitochondrial biogenesis and cellular energy metabolism. In this work, we identified several pathways activating neuronal growth also co-activate PGC-1 α to promote mitochondrial biogenesis to support the energy needs of up-coming growth. In addition, we showed that mitochondrial biogenesis is rate limiting factor for axonal growth and neuronal development.

Eno-Martin Lotman

North Estonia Medical Centre, Cardiology

An 81-year old female patient was admitted to a general cardiology ward, intensive care unit due to acute chest pain that had started 11 hours earlier and had receded slowly. On admission, the patient was almost pain-free on a nitroglycerine continuous infusion. Due to elevated troponins and ECG changes, the patient was diagnosed with a NonSTEMI and was started on appropriate anti-platelet and anti-coagulant therapy. The patient had used statins and beta-blockers before and these were continued. Due to low risk (as per GRACE risk score) the patient was stratified to non-urgent invasive strategy. During the night in the intensive care unit the patient started acting irrationally, complaining and removing cannulas and stating that the medical personnel were abusive (which was incorrect). During the early morning hours the patient started screaming and did not respond to verbal calming. Due to these symptoms, the patient was diagnosed with acute intensive care unit psychosis and started with i/v Haloperidol. In the morning the patient was non-cooperative and therefore could not undergo coronary angiography. With conservative care the patient recovered from the NonSTEMI and acute psychosis and was discharged in a satisfactory general condition.

Mari Urb

Bio- and Translational Medicine, Pharmacology

Corticosterone (CORT) is the main glucocorticoid hormone involved in stress responses in rodents. Our aim is to evaluate the effect of CORT and maternal separation on DNMTs expression. In rat primary cortical neurons, CORT treatment increased mRNA of DNMT3A and DNMT3B. GR antagonist mifepristone significantly decreased CORT-induced DNMTs mRNA. In rat cortex, higher mRNA of DNMT1, DNMT3A and DNMT3B and increased plasma CORT levels were detected. Our results indicate that DNMTs are downstream targets of GR-dependent CORT stimulation and early life stress may induce aberrant DNA methylation pattern that could create conditions for long-term changes in gene expression.

Mari-Liis Laanetu

The North Estonia Medical Centre Psychiatry Clinic, General psychiatry department

68 year old female patient was diagnosed with schizoaffective disorder in her thirties. During her illness she had fairly good compliance and she needed hospitalization relatively rare, last time she was hospitalized in manic state in 2009. In October 2014 she appeared acute neurological symptoms and was diagnosed extensive leftsided intracerebral hemorrhage, comorbid hypertension and hypercholesterolemia. Patient was treated in neurology department and later in rehabilitation department, she left with moderate hemiparesis and minimal aphasia and was also diagnosed cognitive impairment (not specified).

Few weeks before current hospitalization she was presenting inadequate behaviour. In admission she was presenting dementia syndrome, manic symptoms and delusional thoughts, she did not

remember her neurological deficit. What are the diagnosis? What is the main diagnose? Which are the treatment options?

Mailis Liiv

Institute of Biomedicine and Translational Medicine, Department of Pharmacology

Wolfram syndrome 1 (WFS1; OMIM 222300) is a rare genetic disorder which has been associated both with impaired early brain development and neurodegeneration. Wolframin (Wfs1) has been shown to participate in the regulation of Ca²⁺ homeostasis and endoplasmatic reticulum (ER) stress response. Although Wfs1 is an ER membrane protein the clinical manifestations of WFS1 suggest involvement of mitochondrial dysfunction in the course of the disease. Therefore our aim was to examine the hypothesis that Wfs1 deficiency could disturb mitochondrial dynamics leading to impaired neuronal functioning in rat primary cortical neurons. First we show that in Wfs1 deficiency mitochondrial dynamics is altered and both neuronal survival and development are impaired in Wfs1 deficiency and the latter seems to be related to loss of mitochondria by increased mitophagy. We further elaborate that the impairment of mitochondrial dynamics is related to mild ER stress leading to Inositol 1,4,5-Trisphosphate Receptor (IP3R) dysfunction decreasing IP3R related Ca²⁺ release from ER to cytosol and disturbed cytosolic Ca²⁺ levels.