ECNP Seminar in Neuropsychopharmacology

29/03/2019 – 31/03/2019
Palanga, Lithuania

Local organizers:

Psychiatry Clinic at Lithuanian University of Health Sciences
Lithuanian Society of Biological Psychiatry
Young Psychiatrist Association

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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, 21 symposia, 7 educational update sessions and 7 alternative format sessions. The annual meeting attracts around 5,000 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, 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 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 ECNP Seminars in Poland, Estonia, Turkey, Bulgaria, Slovak Republic, Hungary, Czech Republic, Moldova, Romania, Greece, Latvia, Macedonia, Armenia, Georgia, Serbia, Lithuania and recently in Ukraine, Cyprus and the Russian Federation. In some countries we have organised an ECNP Seminar 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 and since 2012 a school of child and adolescent neuropsychopharmacology in Venice. Since 2015 a Workshop on Clinical Research Methods takes place yearly in Barcelona, Spain.

ECNP will also continue the successful 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 relationship 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 Palanga!

Gil Zalsman
Chair ECNP Educational Committee

PROGRAMME

FRIDAY 29 MARCH 2019

Arrival of participants and experts

19.00 Welcome and dinner

SATURDAY 30 MARCH 2019

09.00 – 09.15 What is ECNP?
Introductions to the programme
Speaker: Joseph Zohar (ECNP Seminar Leader)

09.15 – 10.00 NbN - Neuroscience based Nomenclature and research questions in Pre-clinical and Clinical studies
Speaker: Joseph Zohar

10.00 – 10.45 The NOS1/NOS1AP complex as an example of translational research in psychiatry
Speaker: Andreas Reif

10.45 – 11.30 Coffee break

11.30 – 12.15 Addiction research as a model for research plan and design
Speaker: Wim van den Brink

12.15 – 12.30 How to prepare a scientific presentation
Speaker: Joseph Zohar

12.30 – 13.30 Lunch

Presentation participants in 3 groups in 3 parallel workshops			
Round 1 13.30 – 15.00	Joseph Zohar and Vesta Steibliene **Group 1**	Andreas Reif and Virginija Adomaitienė **Group 2**	Wim van den Brink and Kastytis Šmigelskas **Group 3**

15.00 – 15.15 Coffee break

15.15 – 15.45 Panel discussion: How to prepare a clinical research project and how to publish it
Chair: Joseph Zohar
Panel members: Andreas Reif & Wim van den Brink

16:00 – Cultural event, group photo

19.00 –21.00 and dinner at Fish restaurant

SUNDAY 31 MARCH 2019

Presentations participants in 3 groups in 3 parallel workshops

Presentations participants in 3 groups in 3 parallel workshops			
Round 2 08.30 – 10.00	Wim van den Brink and Kastytis Šmigelskas **Group 1**	Joseph Zohar and Vesta Steibliene **Group 2**	Andreas Reif and Virginija Adomaitienė **Group 3**
10.00 – 10.30 Coffee Break			
Round 3 10.30 – 12.00	Andreas Reif and Virginija Adomaitienė **Group 1**	Wim van den Brink and Kastytis Šmigelskas **Group 2**	Joseph Zohar and Vesta Steibliene **Group 3**
12.00 – 14.00 Lunch and preparation for plenary session			
Plenary Session 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 Coffee break and faculty selection of Seminar Award winners.
Completion of feedback forms

15.30 – 16.00 Award ceremony, concluding remarks and thanks
Joseph Zohar and Vesta Steibliene

FACULTY

JOSEPH ZOHAR (SEMINAR LEADER)

Dr. Zohar is a professor of Psychiatry at the Sackler Faculty of Medicine, Tel Aviv University. Dr. Zohar is a past-President of the European College of Neuropsychopharmacology (ECNP). He is also chair of the Israeli consortium on PTSD, and chair of the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). Dr. Zohar is a board member for the International Master in Affective Neuroscience, a visiting Professor at the University of Maastricht (The Nederlands).

ANDREAS REIF

Andreas Reif studied Medicine from 1993 to 2000 at the University of Würzburg. Having decided that he wanted to work in the field of clinical neuroscience, he obtained his doctorate at the Department of Pharmacology (Supervisor: Prof. Dr. H.H.H.W. Schmidt), working on the catalytic mechanism of nitric oxide synthase type I (NOS1). He subsequently specialized in psychiatry, where - from early on - he complemented clinical work with research projects.

During his clinical education at the Department of Psychiatry, University of Würzburg, he joined the research group of Prof. Klaus-Peter Lesch, where he initially focused on the genetic underpinnings of emotions and studied those in animal models. From 2003 onwards, he shifted his focus to adult ADHD, which is still one of his major areas of interest and expertise. In the last 15 years, he has intensively studied the neurobiological basis of this disorders. In doing so, he became a member of a tight network of researchers from many parts of the world, collaborating in the IMpACT consortium and the ECNP Network ADHD across the Lifespan, both of which he co-founded and co-leads.

His second phenotype of interest are mood and anxiety disorders - especially bipolar disorder, depression, and panic disorders. During his work at the University of Würzburg, he got promoted several times up to the level of Vice Chair. In 2014, he moved to Frankfurt am Main, where he took over the Chair position of the Department of Psychiatry, Psychosomatic Medicine and Psychotherapy and established sections on Translational and Experimental Psychiatry. He serves in important positions on the boards of several societies, the most important ones being the DGPPN and ENCP. He currently coordinates the EU-funded CoCA consortium and is a work package leader in several additional EU-funded consortia. Andreas Reif has published more than 350 papers with a cumulative impact factor > 2.000 and amounting to an h factor of 61.

WIM VAN DEN BRINK

Wim van den Brink (1952) received his medical degree in 1981 from the Free University in Amsterdam. After his training as a psychiatric epidemiologist in Groningen (1983-1986) and New York (1986-1987) he received his PhD degree form the State University of Groningen in 1989. Since 1992 he is full professor of Addiction Psychiatry at the Academic Medical Center of the University of Amsterdam. He is also the director of the Amsterdam Institute for Addiction Research (AIAR). In 2014 he received the life time achievement award for science from the Netherlands Association of Psychiatry and in 2015 he was granted the status of honorable member of the Spanish Society for Dual disorders. In 2017 he received the European Addiction Research Award from the European Federation of Addiction Societies (EUFAS). He is a (co)author of more than 500 international peer reviewed scientific papers (HI WoS=66; HI Google Scholar=92). He has been a thesis advisor of 75 PhD students. He recently stepped down as one of the chief-editors of European Addiction Research. He has been the chair of the Workgroups that developed the Dutch Treatment Guidelines on Alcohol Use Disorders, the Dutch guideline on Opiate Addiction and the Dutch guideline on Drugs other than opioids. He is one of the founders and president of the International Collaboration of ADHD and Substance Abuse (ICASA). He was the chair of the Scientific Program Committee of European College of Neuropsychopharmacology (ECNP). His main scientific interests are related to the neurobiology of substance use disorders and behavioral addictions, the pharmacological treatment of substance use disorders and related comorbidities, and the reduction of stigma regarding patients with an addiction.

PRESENTATIONS

JOSEPH ZOHAR

HOW TO PREPARE A SCIENTIFIC PRESENTATION

ECNP European college of neuropsychopharmacology

How to prepare a scientific presentation

Joseph Zohar

ECNP

Learning

- Definition of *any* kind of learning?

Learning

- Definition of *any* kind of learning= a steady change in behavior as a result of an experience
- The change has to happen in your audience
- Effective learning is an active process

Before you start

- Who is your audience?
- What is your desired outcome?
- How much time do you have?
- What are the key messages?
- Is your PP presentation working?

Common Causes of Ineffective Presentations

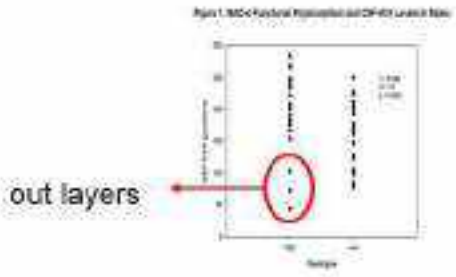
- Failure to prepare the talk
- Cut and paste from your paper
- Gaps in logic
- Poor delivery (speaker)
- Poor time planning
- Too many slides

Organising a Presentation

I. Outline
II. Problem and background
III. Design and methods
IV. Major findings - the heart of your talk
V. Conclusion, limitations and recommendations

Major Findings

- Text and or table/graph
- One slide for each
- Message should be clear
- Figures are the best



Conclusion and Recommendations

- What have we learnt?
- Key points
- Clinical Implications
- Clear closure (pause, high note, thanks)

Making Slides

- Main points only
- One idea per slide
- Few words (5-10 per line)
- Strong statements: active voice
- 1 slide per 1 minute

Making Slides *(Continued)*

- Type size should be 24 points or larger:

18 point

20 point

24 point

28 point

36 point

- References can be in 14 point font

Making Slides *(Continued)*

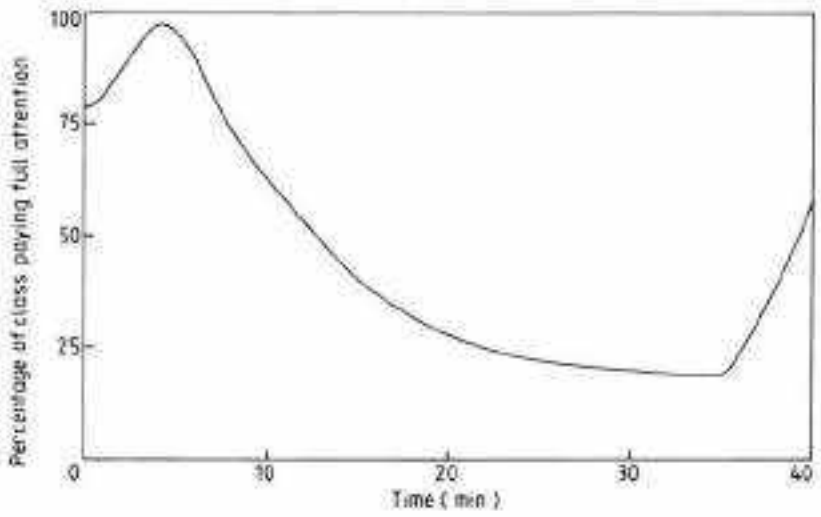
- Best contrasts

Yellow on Blue

or

Black on White

Audience Attention Curve



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ANDREAS REIF

THE NOS1/NOS1AP COMPLEX AS AN EXAMPLE OF TRANSLATIONAL RESEARCH IN PSYCHIATRY

Nitric oxide (NO) is a highly unusual, gaseous transmitter in the brain, which has been implicated in a wide range of neurobiological functions. Soon after the discovery of its synthesizing enzyme, nitric oxide synthase 1 (NOS-I), it was speculated whether it also might play a role in the pathogenesis of mental disorders. First evidence came from knockout mice, that displayed by highly aggressive behavior. Also, pilot data suggested that NOS-I neurons show abnormalities in schizophrenia. To investigate whether NO, or NOS-I respectively, is involved in schizophrenia and impulsive-aggressive behaviors including ADHD, I chose a translational approach by both studying the consequences of manipulated NOS-I expression in mice as well as characterizing the effects of polymorphisms in the NOS1 gene regarding disease status and also neuroimaging data. Intriguingly, Nos1 knockout mice feature a distinct behavioral phenotype reminiscent of ADHD; however, their behavioral pattern seems to be variable across laboratories. Manipulations of NOS-I at the glutamatergic post-synapse on the other hand goes along with schizophrenia-like behavior. In the human NOS1 gene, there are two functional polymorphisms which affect gene expression. While on of them, NOS1 ex1f-VNTR was initially associated with ADHD, this could not be clearly replicated in larger samples although the polymorphism was also correlated with neuroimaging measures of impulsivity. Equally complex was the association of a SNP in exon 1c, which was found to be associated in some, but not all tested samples; nevertheless, NOS1 still holds up as a viable candidate gene. Taken together, there is promising evidence that genetic variation in the NO

system is linked to psychiatric disorders but owing to the complexity of both mental diseases as well as the neuronal transcriptome, we are still far from making definitive conclusions.

The NOS1/NOS1AP complex as an example of translational research in psychiatry

A. Reif / Department of Psychiatry, Psychosomatic Medicine and Psychotherapy / German Center for Developmental Psychiatry

Dept. of Psychiatry, Psychosomatic Medicine & Psychotherapy, University Hospital Frankfurt

F. Freudenberg

E. Candemir

A. O'Leary

J. Kopf

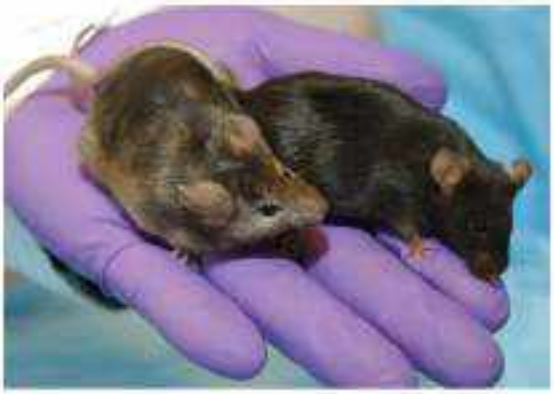
H. Weber

Dept. Psychology, Tartu

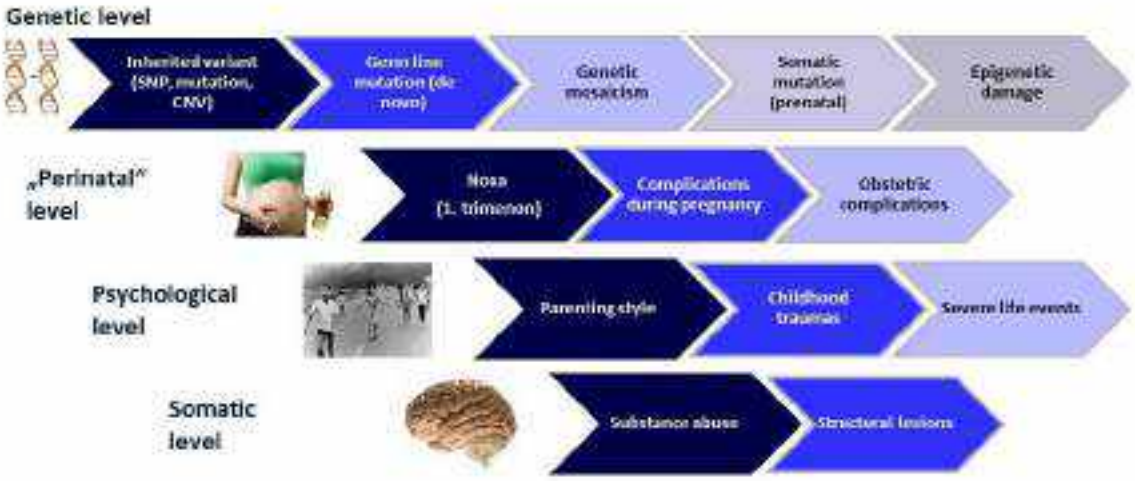
J. Harro and colleagues

Donders Institute
Nijmegen / Radboud MC

B. Franke
and colleagues



Complexity of psychiatric disorders



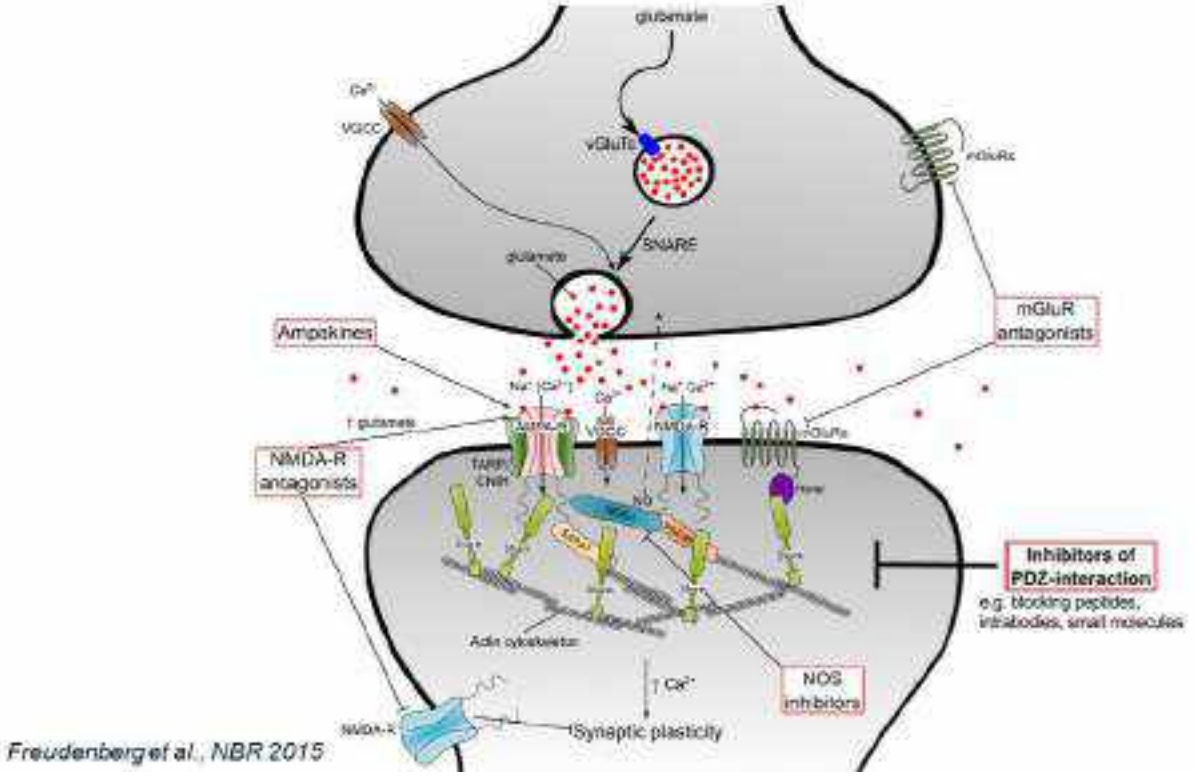
- Interaction between all levels
- Common downstream mechanisms (phenocopies)
- Inaccessibility of the brain

Reif & Freitag, JNT 2016

Nitric oxide (NO): a gaseous messenger

- **Nitric oxide (NO):** gaseous radical, free diffusion in biological tissue, operating diameter ~ 300 µM, half life ~ 5 s
- Synthesis by 3 isoforms of NO synthases
  - „neuronal" NOS-I (ca. 1 % of all neurons contain NOS-I)
  - „inducible" NOS-II
  - „endothelial" NOS-III
- High expression of NOS-I in the hippocampus, cortex, and the basal ganglia
- Second messenger of the NMDA receptor
- Messenger in low concentrations – neurotoxic in high concentrations

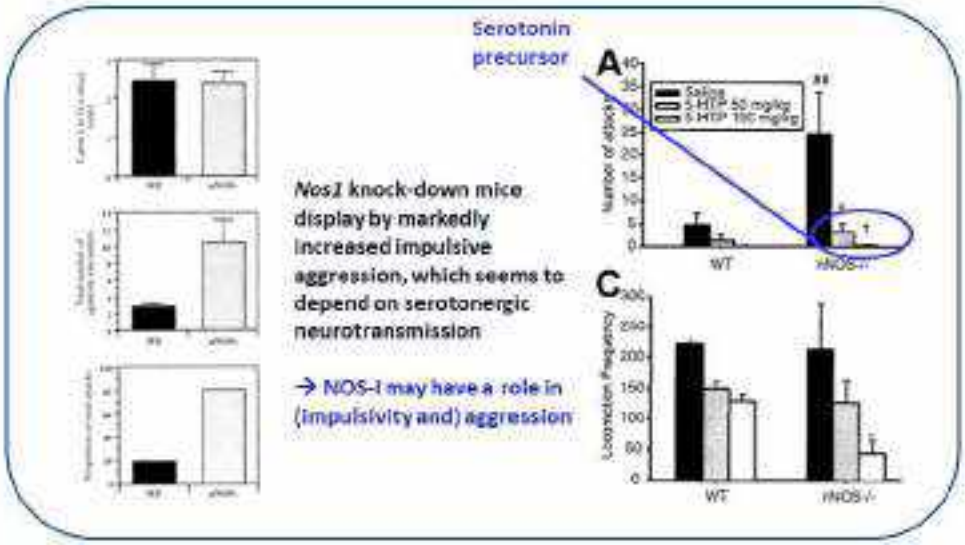
The NMDAergic:nitrinergic synapse



Freudenberg et al., NBR 2015

How I came into NO research

First clues for a role of NOS in mental disorders: behavioral studies with *Nos1* knockdown mice



Nos1 knock-down mice display by markedly increased impulsive aggression, which seems to depend on serotonergic neurotransmission

→ NOS-I may have a role in (impulsivity and) aggression

Nelson et al., Nature 1995; Chiavegatto et al., PNAS 2001

However the *knockdown* phenotype varies widely...

Test	NOS-I knockdown
General	
Sensorimotor screening/ observation	Increased touch-escape reaction, body position, locomotion, elevation and reduced vocalizations, increased grooming — "autistic like behaviour" (Weitendorfer et al., 2005)
Pole/plank test (balance/ coordination)	No/normal impairment (Klingelhöfer et al., 1999); no difference (not shown; Nelson et al., 1995))
Rotarod	No difference (Chiavegatto et al., 2001); no difference (Kirchner et al., 2004); **No difference**
Hotplate (pain sensitivity)	Increased sensitivity to pain (Nelson et al., 2006); unpublished); **No difference**
Activity & Novelty	
Open field	More active during the active cycle, more time spent in center of the open field (Bilbo et al., 2003); no difference (not shown; Nelson et al., 1995)); more center crossings and more center entries (Weitendorfer et al., 2004); normal (Chiavegatto et al., 2001); Higher center time/crossings (Kirchner et al., 2005); No difference (Salchner et al., 2004); **No difference**
Novelty seeking	**No difference**
Emotionality & Depression	
Light Dark-Box	**No difference**
Forced	Reduced immobility time (Salchner et al., 2004); fewer depression-like responses (Nelson et al., 2006; unpublished); **No difference**
Learned helplessness	**No difference**
Tail suspension	n.p.
Novel cage	**No difference**
Elevated plus maze	No difference (Bilbo et al., 2003); more time spent in closed arm (Weitendorfer et al., 2004); more entries in closed arm (Kirchner et al., 2005); **Higher open arm time**

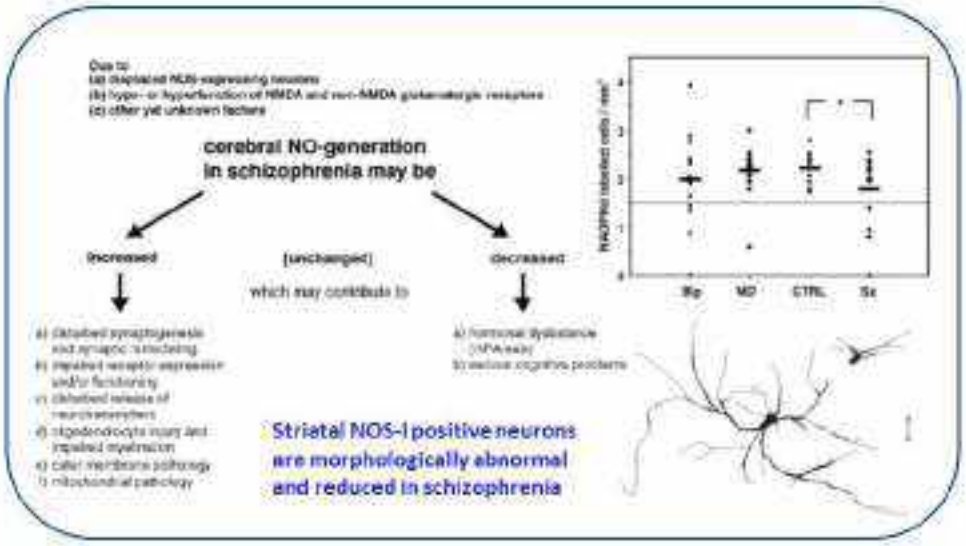
Maze & Learning	
COCTAT/Icebreaker	**Impaired spatial learning**
8-Arm radial maze	n.p.
Morris water maze	Worse performance (Weitendorfer et al., 2004); worse performance (Kirchner et al., 2004); **Impaired spatial learning**
T-Maze	Better performance (Weitendorfer et al., 2004)
Aggression & Maternality	
Resident-intruder aggression	Males – increase (Nelson et al., 1995), testosterone dependent (Klingelhöfer et al., 1997); not in BL/6 back-crossed mice (Le Roy et al., 2006)
Neural aggression	Males – increase (Nelson et al., 1995), testosterone dependent (Klingelhöfer et al., 1997); not in BL/6 back-crossed mice (Le Roy et al., 2006)
Maternal aggression	Absent (Gammie and Nelson, 1999)
Maternal behavior	Otherwise no difference (Gammie and Nelson, 1999)
Stress	
Baseline corticosterone	Higher in knockout mice (Bilbo et al., 2003)
Stress-induced increase	Disrupted corticosterone response in knockout animals (Bilbo et al., 2003)

Consistently:
kd's have increased activity and impaired learning

Unclear: role in aggression and anxiety

Wultsch et al., JNT 2007

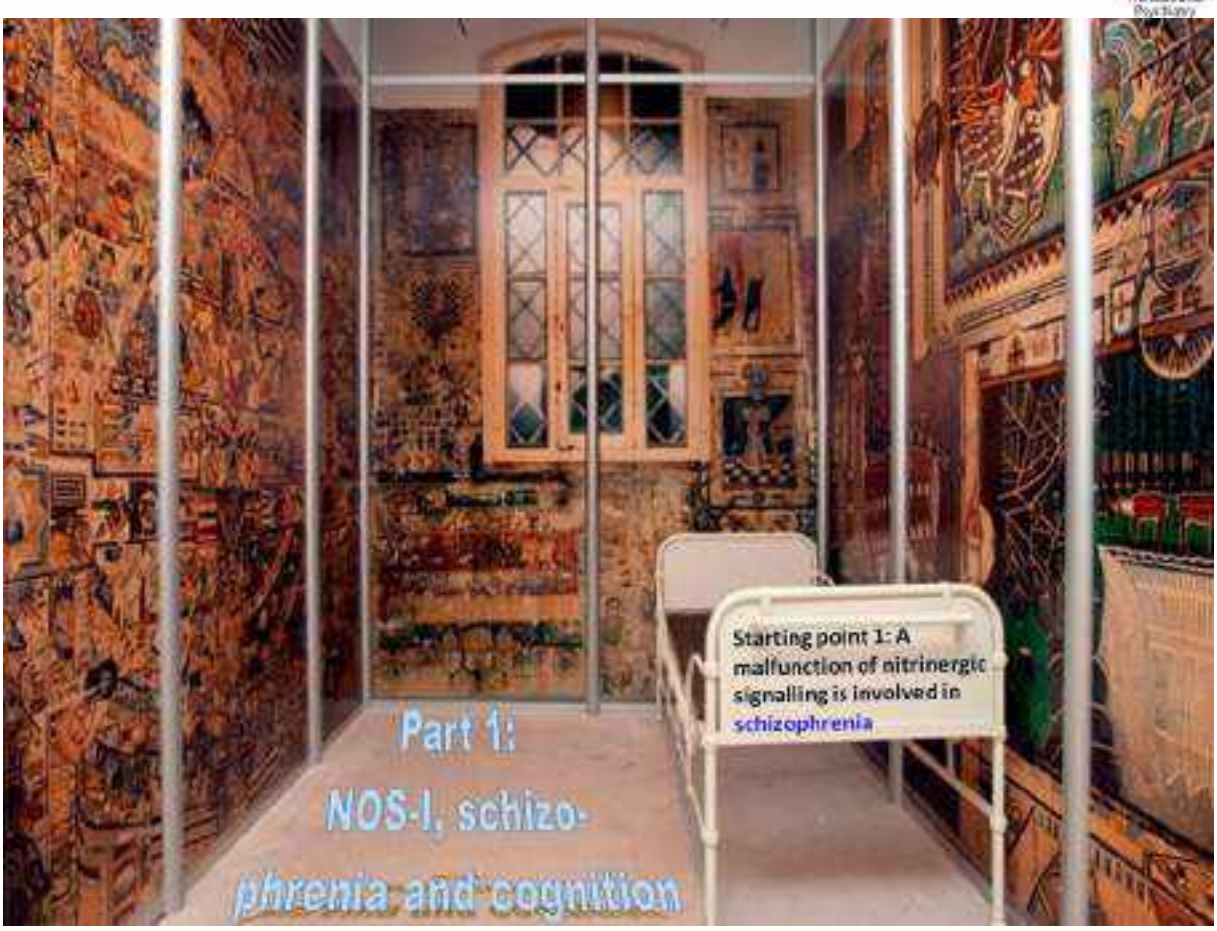
First clues for a role of NOS in mental disorders: post-mortem studies in schizophrenia



Bernstein et al., Schizo Res 2005; Lauer et al., Neuropsychobiol 2005; Fritzen et al., ENPP 2007

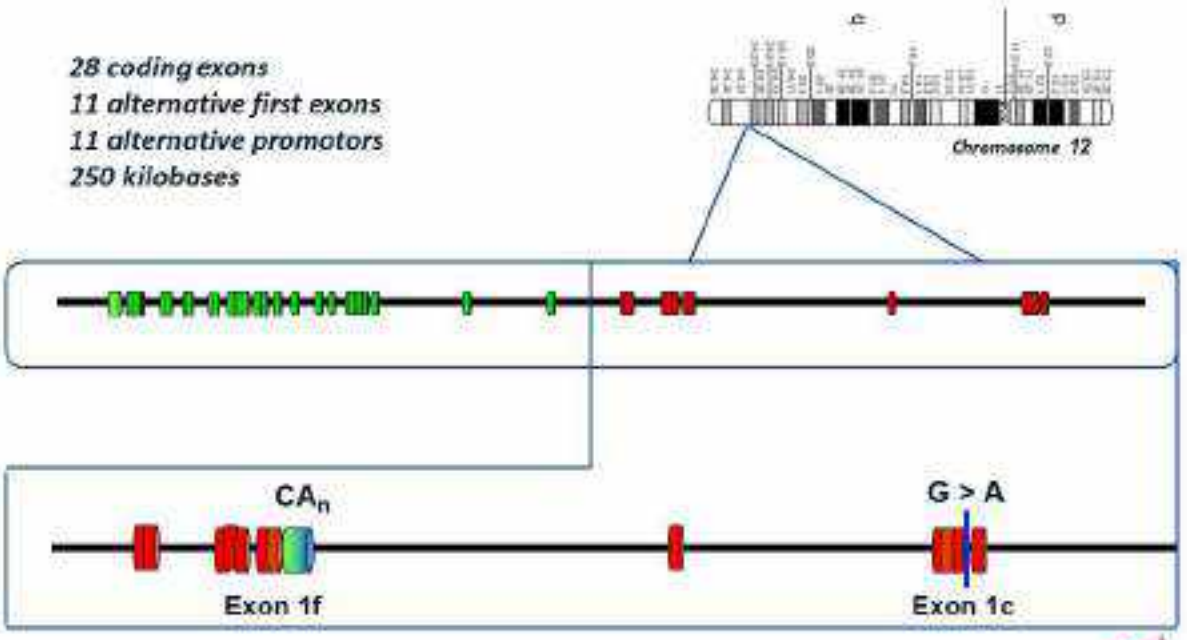
Two starting points:

- A malfunction of nitrinergic signalling is involved in schizophrenia
- Genetically induced reduction of NOS-I is involved in impulsivity / aggression (→ ADHD)



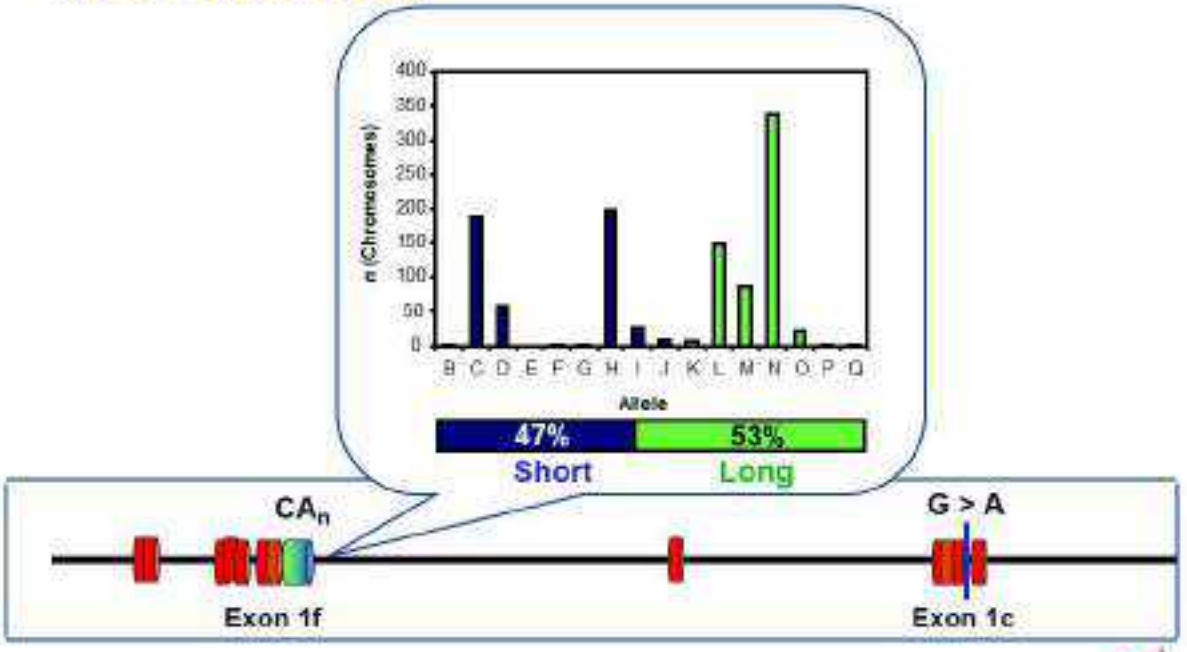
The human *NOS1*-Gene (12q24.2-.31)

28 coding exons
11 alternative first exons
11 alternative promotors
250 kilobases



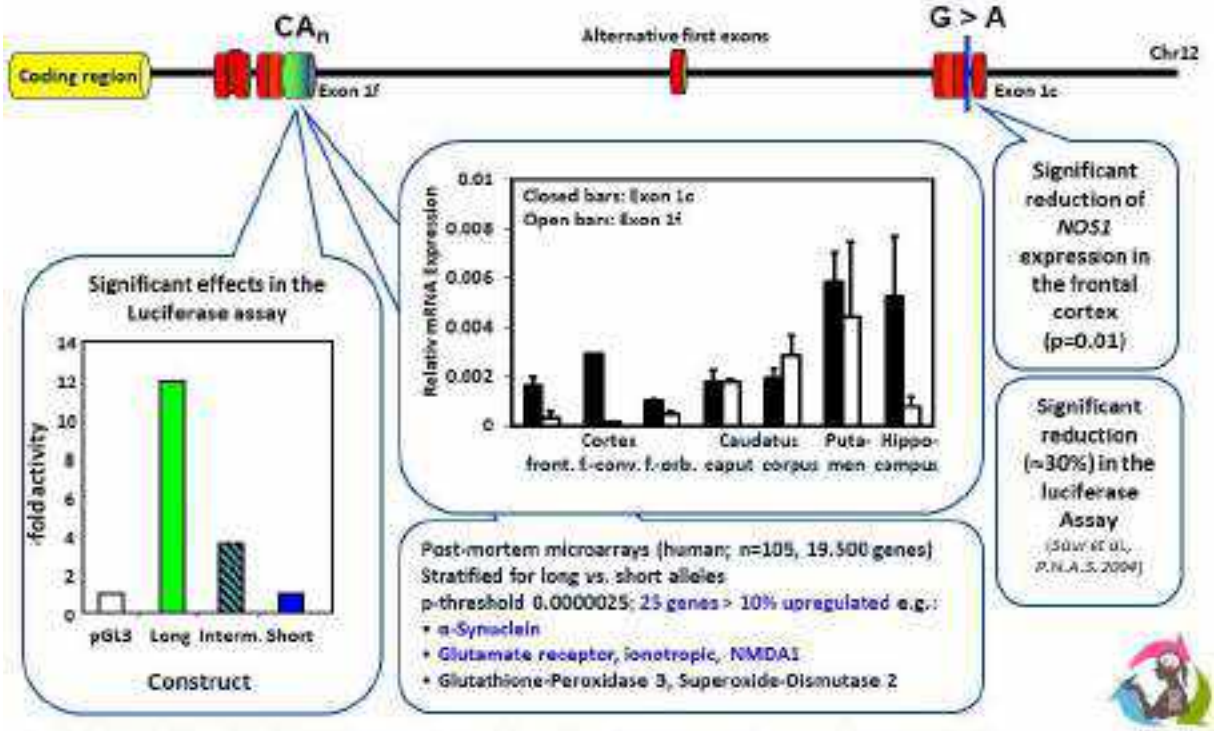
Reif et al., Arch Gen Psychiat 2009; Freudenberg et al., GBB 2015

NOS1-ex1f VNTR



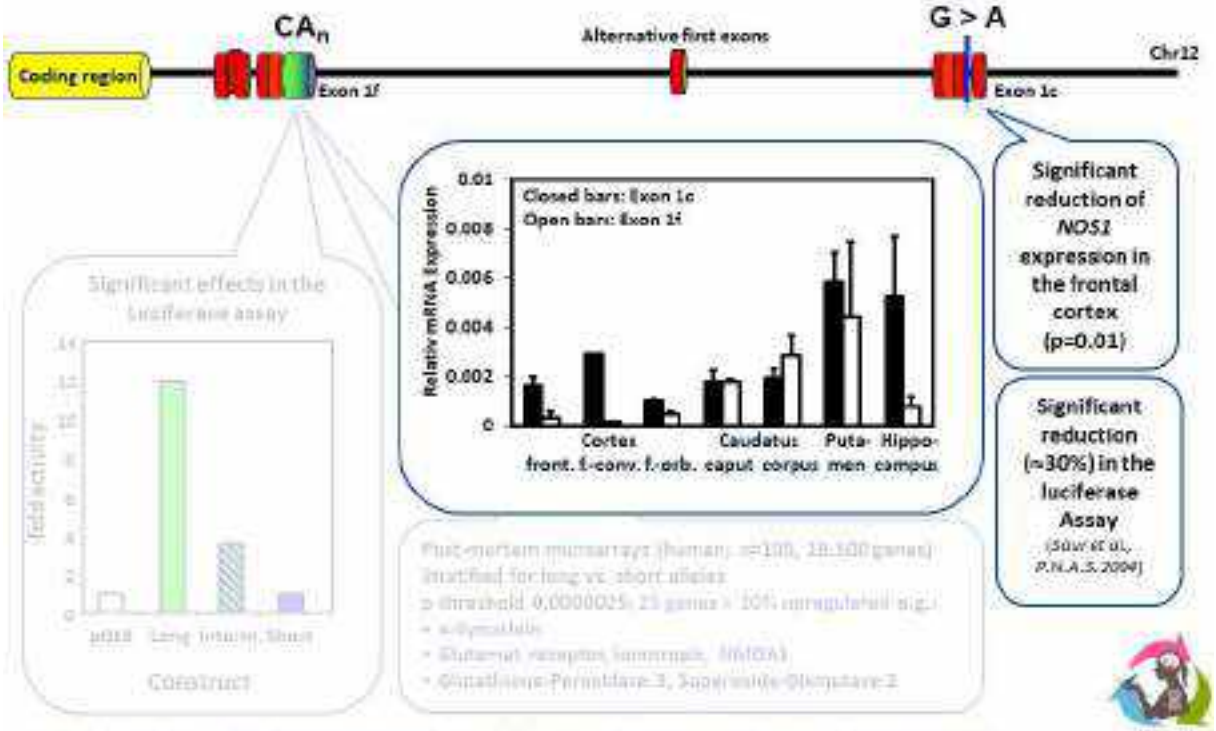
Reif et al., Mol Psychiat 2006; n = 5716 chromosomes (healthy controls)

Regulation of *NOS1* expression in the brain



Reif et al., Mol Psychiat 2006; Reif et al., Arch Gen Psychiat 2009; Weber et al., EJNPP 2014

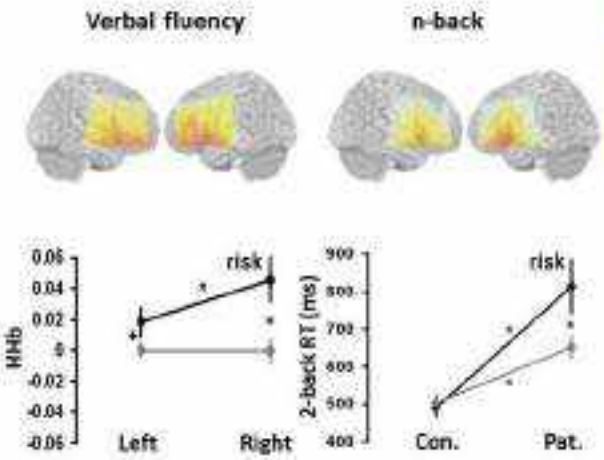
Regulation of *NOS1* expression: exon 1c

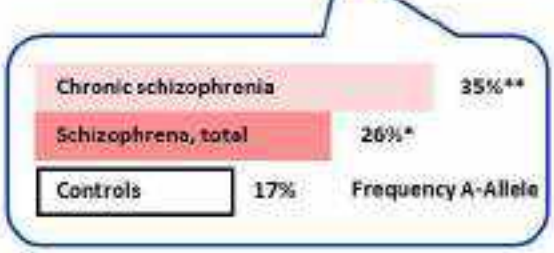


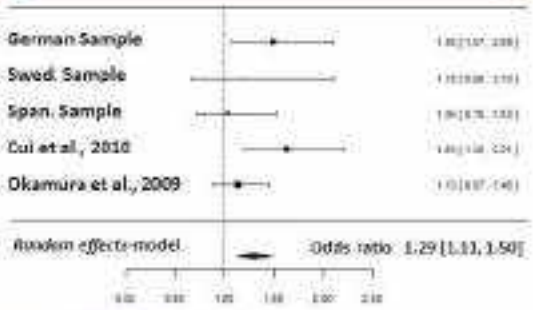
Reif et al., Mol Psychiat 2006; Reif et al., Arch Gen Psychiat 2009; Weber et al., EJNPP 2014

NOS1-Ex1c rs41279104, scz and cognition

Controls vs. patients, fNIRS



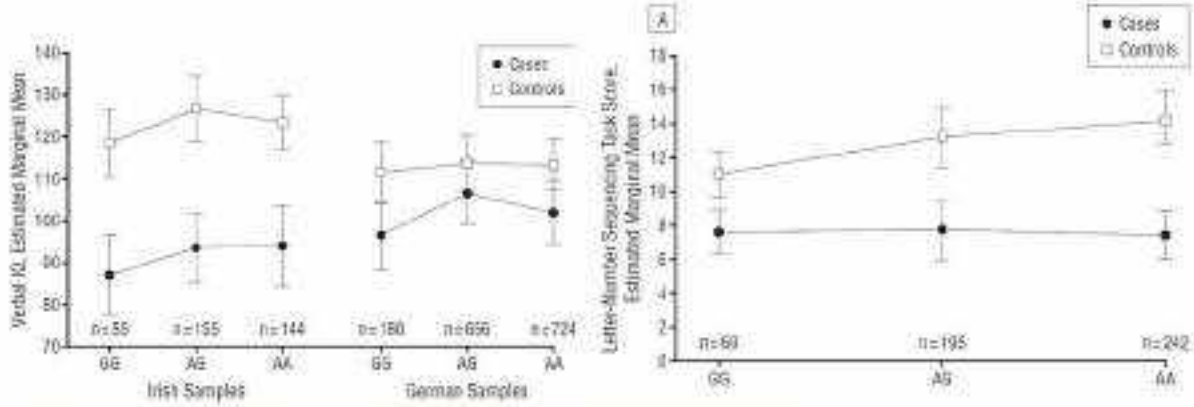




Reif et al., Mol Psychiat 2006; Reif et al., IJNP 2010; Weber et al., EJNPP 2014

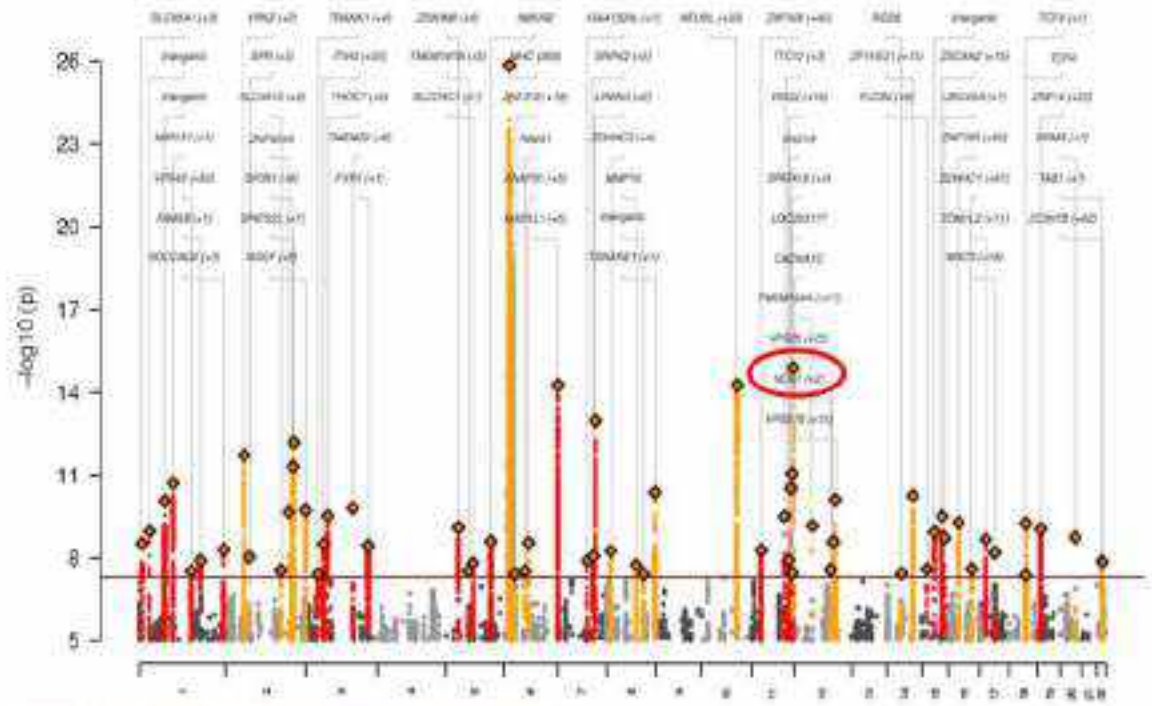
NOS1: one of the first GWAS Top Hits (rs6490121)

			Combined UK samples					Replication 1		Replication 1+2		Meta SZ			
			Cases n = 642 Controls n = 2,937					Cases n = 1,664 Controls n = 3,541		Cases n = 6,665 Controls n = 9,897		Cases n = 7,305 Controls n = 12,834			
Chr./Kb	SNP	Risk allele	SZ	CON	ATT(P)	Adj(P)	OR	CMH(P)	OR	CMH(P)	OR	CMH(P)	Meta Adj.	OR	Locus
2/185.9	rs1344706	T	0.66	0.59	7.08×10^{-7}	1.83×10^{-6}	1.39	0.026	1.09	9.23×10^{-5}	1.09	1.61×10^{-7}	1.95×10^{-7}	1.12	ZNF804
11/29.1	rs1602565	C	0.15	0.11	7.81×10^{-6}	1.70×10^{-5}	1.49	0.005	1.19	3.22×10^{-4}	1.12	2.99×10^{-7}	3.02×10^{-7}	1.16	Intergenic
16/13.0	rs7192086	T	0.30	0.24	3.32×10^{-5}	6.52×10^{-5}	1.33	0.018	1.11	5.10×10^{-4}	1.09	6.08×10^{-6}	1.34×10^{-5}	1.12	Intergenic
11/132.1	rs3016384	C	0.56	0.49	5.82×10^{-5}	1.10×10^{-4}	1.29	0.012	1.10	0.016	1.05	5.63×10^{-6}	1.11×10^{-5}	1.08	OPCML
16/52.2	rs9922369	A	0.05	0.03	8.05×10^{-7}	2.05×10^{-6}	2.06	0.015	1.31	0.029	1.14	4.54×10^{-7}	5.01×10^{-6}	1.24	MPGR/PIC
12/116.2	rs6490121	G	0.40	0.34	4.33×10^{-5}	9.82×10^{-5}	1.33	0.044	1.06	0.992	1.00	0.109	5.51×10^{-5}	1.04	*NOS1*



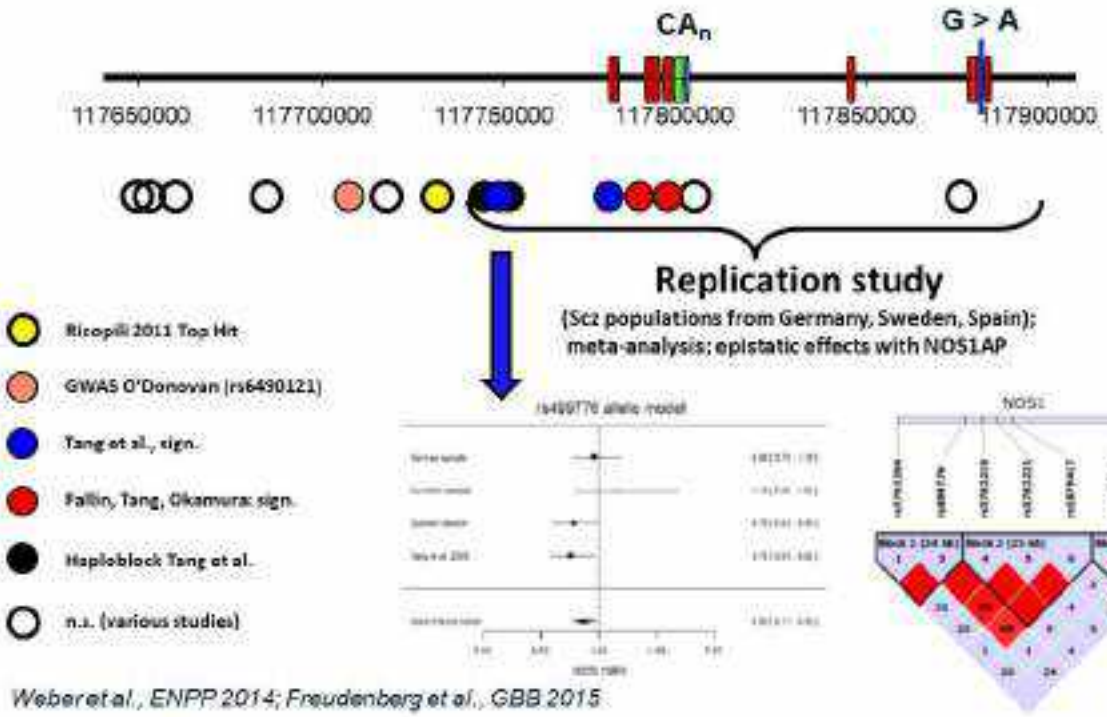
O'Donovan et al., Nat Genetics 2008; Donohoe et al., Arch Gen Psychiat 2009

NOS1: still a GWAS Top Hit



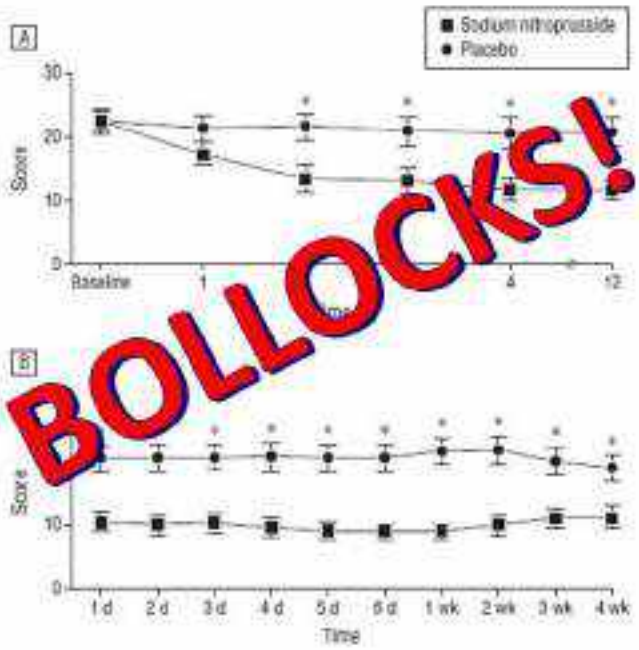
PGC Schizophrenia Workgroup 2013 (interim analysis)

NOS1 and schizophrenia – replication attempts



Weber et al., ENPP 2014; Freudenberg et al., GBB 2015

NO signalling as a therapeutic target in scz?



BOLLOCKS!

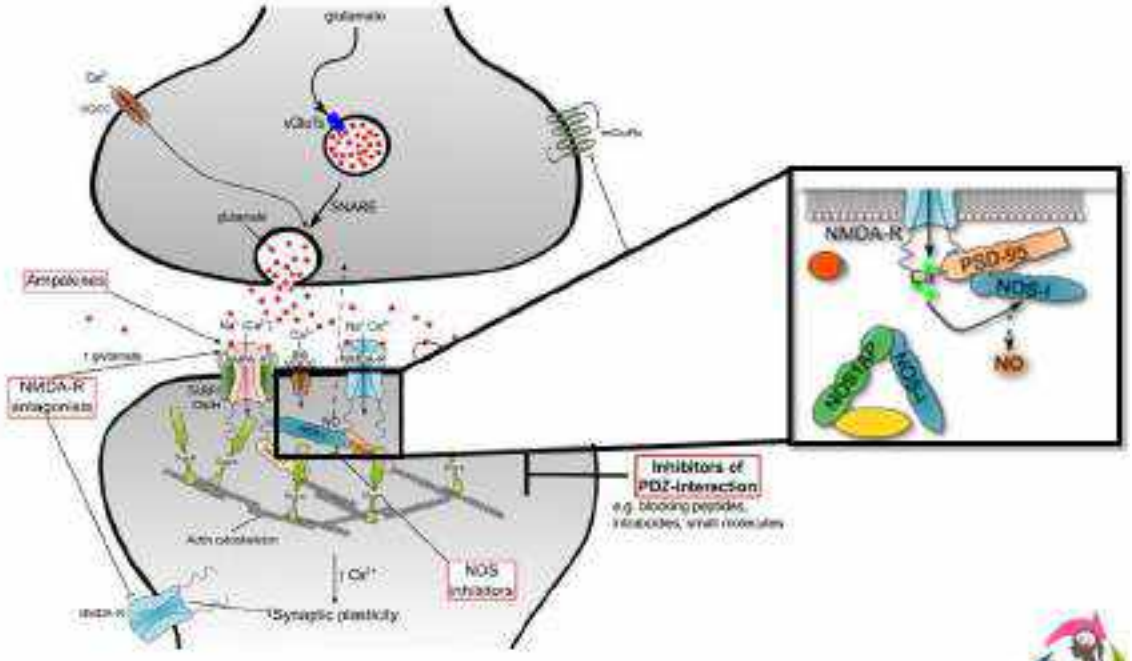
Effector mechanisms?

Effects on cognition?

Genetic stratification of patients?

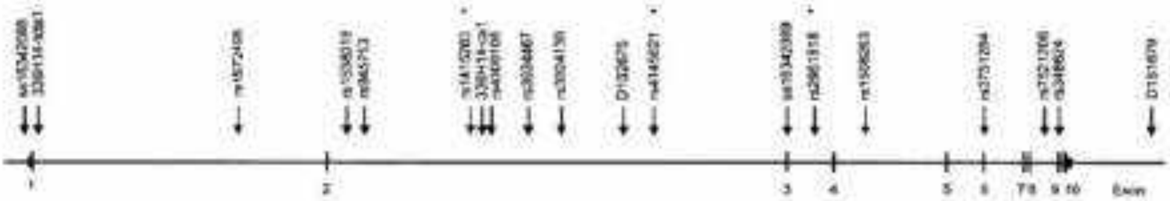
Hallek et al., JAMA Psychiatry 2013

The NMDAergic:nitrinergic synapse: NOS1AP



Freudenberg et al., NBR 2015; Freudenberg et al., GBB 2015

NOS1AP is also a genetic risk factor for schizophrenia

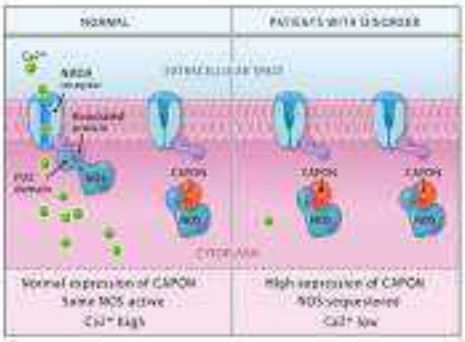


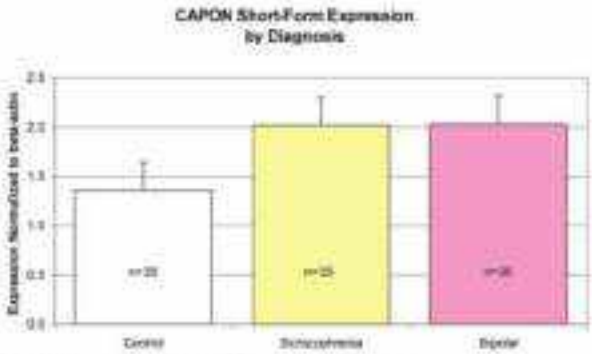
Positional (linkage) ↑ ↓ Functional (case-control)

SNP	Chromosomal allele			German sample				Swedish sample				Spanish sample			
				Number of genotypes		Nominal	Bonferroni	Number of genotypes		Nominal	Bonferroni	Number of Genotypes		Nominal	Bonferroni
	Position (bp)	(a/b)	Association Model	Controls (n=[illegible])	Cases (n=270)	P-value	P-value	Controls (n=[illegible])	Cases (n=[illegible])	P-value	P-value	Controls (n=[illegible])	Cases (n=270)	P-value	P-value
NOS1AP (Capon); Chromosome 1															
[illegible]	[illegible]	T/C	Genotypic [illegible]	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1
			Allelic [illegible]	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1
			Dominant [illegible]	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1
[illegible]	[illegible]	C/G	Genotypic [illegible]	–	–	–	–	[illegible]	[illegible]	[illegible]	1	–	–	–	–
			Allelic [illegible]	–	–	–	–	[illegible]	[illegible]	[illegible]	1	–	–	–	–
			Dominant [illegible]	–	–	–	–	[illegible]	[illegible]	[illegible]	1	–	–	–	–
[illegible]	[illegible]	C/T	Genotypic [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1
			Allelic [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1
			Dominant [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]	1

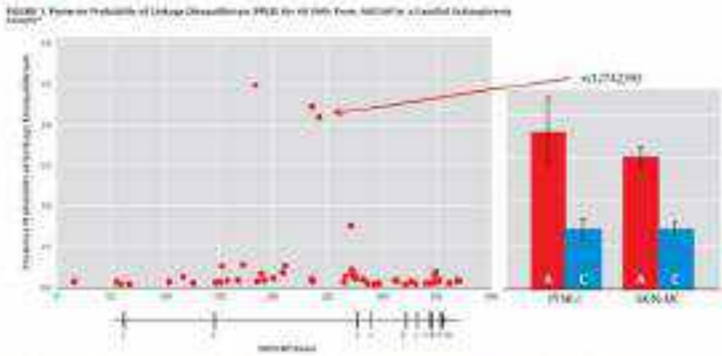
Brzustowicz et al., Am J Med Genet 2004; Weber et al. ENPP 2014

NOS1AP expression is increased in schizophrenia

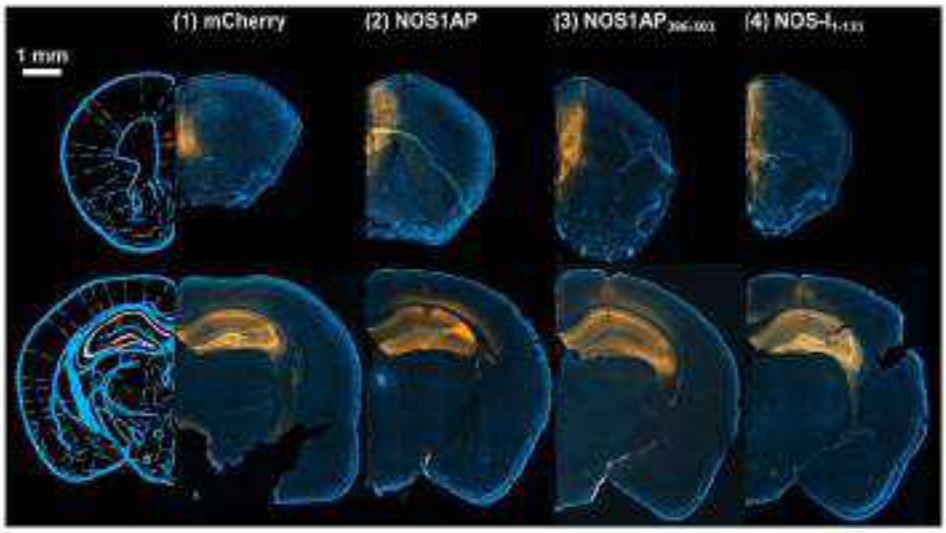




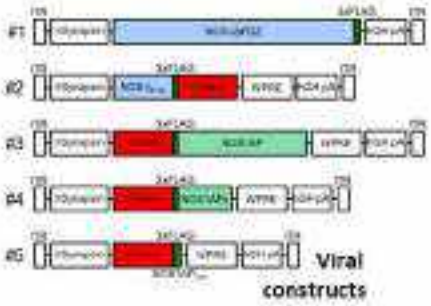
- *NOS1AP* is a positional schizophrenia candidate gene
- Positive case-control studies; epistatic interaction with NOS1 (Weber [...] Reif, 2014)
- Risk SNPs increase *NOS1AP*-expression
- *NOS1AP* expression (*post mortem*) is increased in schizophrenia



Eastwood, PLoS Medicine 2005; Xu et al., PLoS Med 2005 & Wratten et al., 2009 AmJP (Brzustowicz Lab)

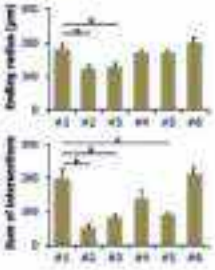


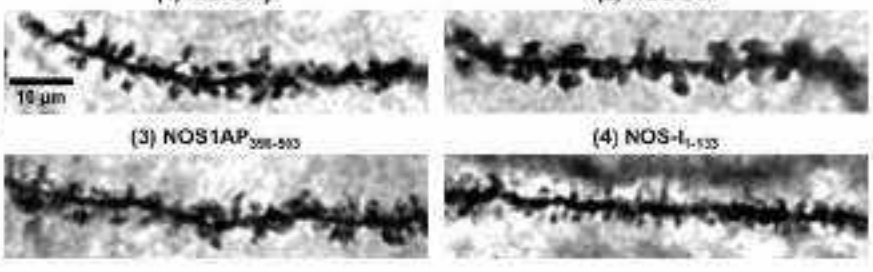
Increased NOS-I <> NOS1AP interaction sequesters NOS-I from the NMDA receptor / reduced NOS-I expression
→ reduced nitrinergic transmission
→ disruption of NOS1AP interaction as a therapeutic principle?



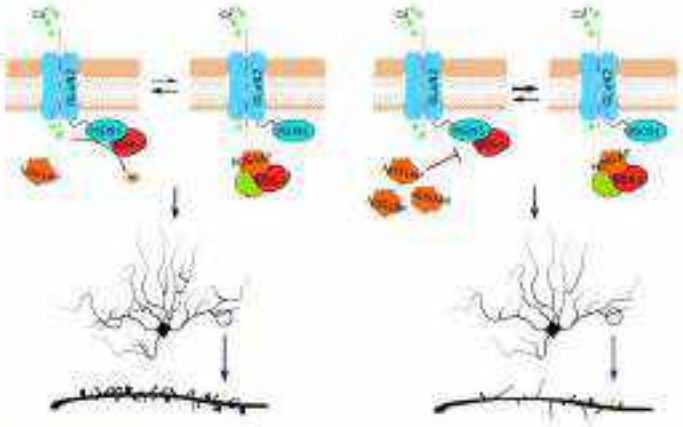
Candemir, O'Leary, Freudenberg & Reif, in prep.

Shell analysis





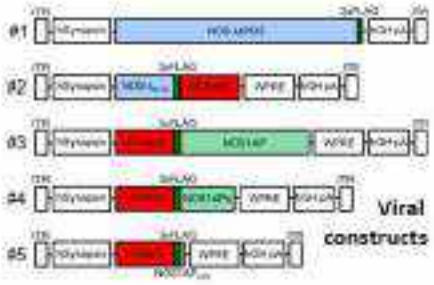
Increased NOS-I <> NOS1AP interaction sequesters NOS-I from the NMDA receptor
→ reduced nitrinergic transmission

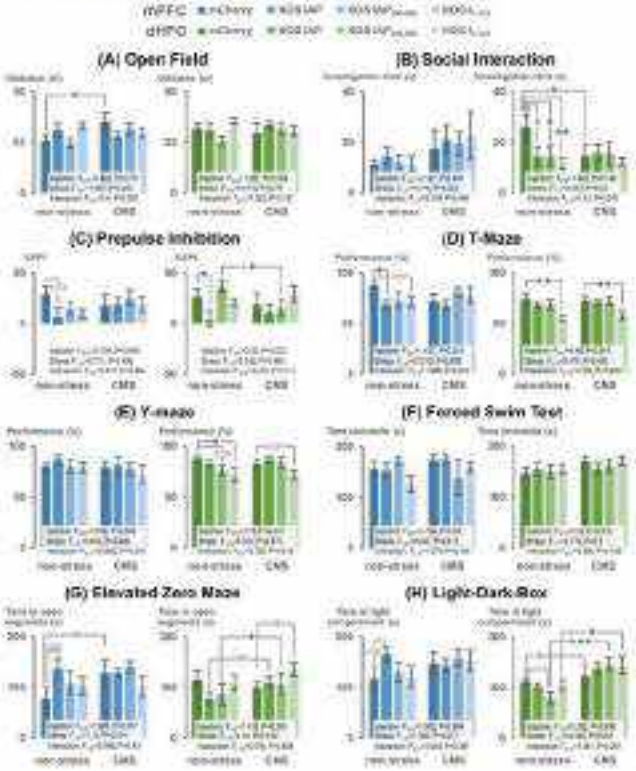


Overexpression of *NOS1AP*:
Scz-typical morphological changes:
- Disturbed spine morphology
- Spine number ↓
- Dendritic branches ↓
- Dendritic spines ↓ ↓

Eastwood, PLoS Medicine 2005
Candemir [...], Reif & Freudenberg, 2016 EurNPP & in prep.

NOS-I<>NOS1AP and behavior





Increased NOS-I <> NOS1AP interaction sequesters NOS-I from the NMDA receptor
→ reduced nitrinergic transmission

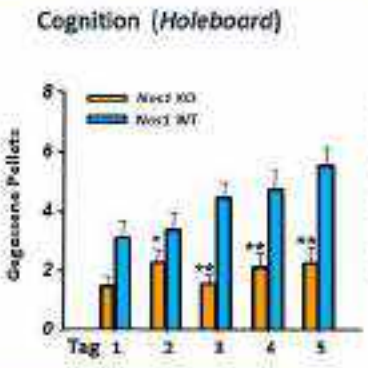
Overexpression of *NOS1AP* in HIP:
Scz-typical behavioral changes:
- Cognitive impairment
- Impaired social interaction
- Anxiety
- PPI disruption

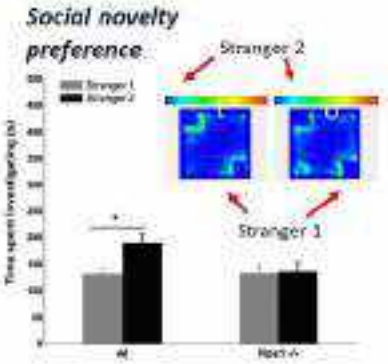
Candemir, O'Leary, Freudenberg & Reif, in prep.

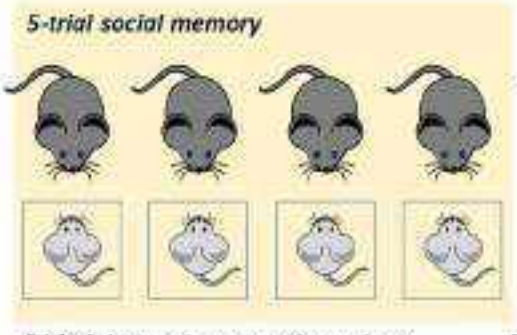
Nos1 knock-down →
reduced nitrinergic transmission

- Spatial learning ↓
- Social interaction ↓↓
- Compulsivity ↑
- Perseverations (5-CSRTT)

Animal model of schizophrenia?







Trial 1-4: 4 x 1 min encounter with a previously unknown 3 wk mouse

Trial 5: 1 min encounter novel 3 wk pup

known mouse

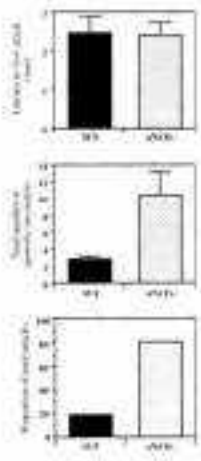
Wultsch [...] Reif, JNT 2007; O'Leary [...] Reif, in preparation

Conclusions (I)

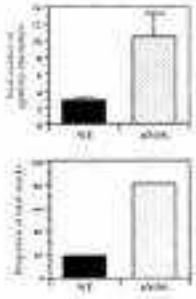
- Compromised prefrontal *NOS1* function: working memory deficits
  Schizophrenia (esp. human data)
- Compromised hippocampal *NOS1* function: PPI, WM, social interaction: schizophrenia (esp. mouse data)
- Supported by human genetic data

Starting point 2: A genetically induced reduction of NOS-I is involved in impulsivity / aggression (→ ADHD)

Part 2: NOS1, impulsivity and aggression



NOS1 and aggressive behaviour



(*aggression, mice*)

N = 184 prison inmates, thereof 72 with violent crimes (homicide, physical injury, robbery); no axis-I disorder
Well documented life history. Outcome variable: violence

	χ^2	p
***NOS1* Exon 1f VNTR short**	**6.2**	**0.04**
Odds ratio SS vs. LL 3.2, SS vs. SL 1.4		
***"Childhood adversity"* (sum score)**	5.1	0.02
Substance abuse	3.9	0.05
Personality disorder	0.1	0.82

No gene x environment interactions were observed.

→ **Short *NOS1* Ex1f-Alleles are associated with violent, aggressive behaviors**

Reif et al., Arch Gen Psychiat 2009; Nelson et al., Nature 1996

NOS1 and suicidal behaviour

In previous studies, risk genes for violent behavior (e.g., 5HTT or MAO-A) were also shown to be linked to suicidal behaviors

→ **Association of *NOS1* ex1f VNTR with suicide?**

N = 1319 healthy controls and N = 189 suicide attempters; affective spectrum (n=130), schizophrenia and borderline PD

	χ^2	p
***NOS1* Exon 1f VNTR short**	**8.3**	**0.01**

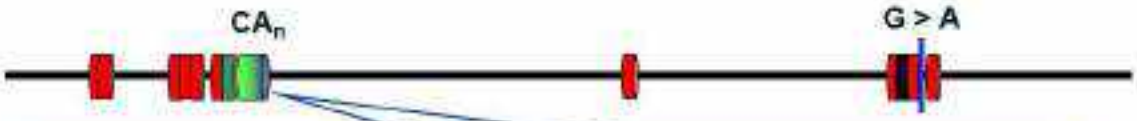
No significant effects of genotype **on suicide phenotype** (violent suicide, probability of death, impulsiveness)

Independent replication: N = 438 patients, thereof n = 142 suicide attempters; schizophrenia spectrum (n=331/69) and affective spectrum (n=107/73).

	χ^2	p
***NOS1* Exon 1f VNTR short**	**1.5**	**0.04**

Reif et al., Arch Gen Psychiat 2009; NPP 2007; unpublished

NOS1 and ADHD



Further evidence for an association of *NOS1* with ADHD: rs478597 was associated with quatitative traits in ADHD in a recent GWAS (GAIN; p=10^{-8}, Lasky-Su 2008, Franke 2009)

Family based ADHD sample; 151 affected children from 101 families. TDT, outcome variable "categorical ADHD"
NOS1 Exon 1f VNTR short transmission rate 0.54, p = 0.391

Case-Control sample with adult ADHD (n=383) and controls (n=469), diagnosed for PD and personality traits.
Outcome variable: aADHD

	χ^2	p
NOS1 Exon 1f VNTR short	**22.1**	**0.002**

But: high Co-Morbidity with PD in this sample!
e.g., **Cluster B PD 27 – 35%**

→ **NOS1 Ex1f increases the risk for persistence of ADHD into adulthood**

Reif et al., Arch Gen Psychiat 2009; Jacob et al., Eur Arch Psychiatry Clin Neurosci 2007

Replication and meta-analysis

IMpACT

Risk factor in females only?
Association rather with impulsivity?

Case-Control sample with adult ADHD (n=383) and controls (n=1963, 19% SS):

	p
NOS1 Exon 1f VNTR short 28%	**0.002**

Replication:
2nd wave of ADHD patients (n=265):
NOS1 Exon 1f VNTR short 23%
Combined sample (n=648):
NOS1 Exon 1f VNTR short 26%

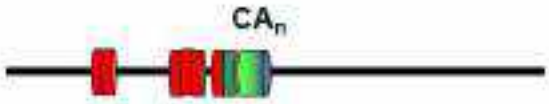
[illegible] (n=77)	19%	(vs. 24%)
Spanish sample (n=301)	24%	(vs. 28%)
Norwegian sample (n=416)	23%	(vs. 22%)

Overall OR 1.03 [95% CI 0.76 – 1.40]

Replication crisis!

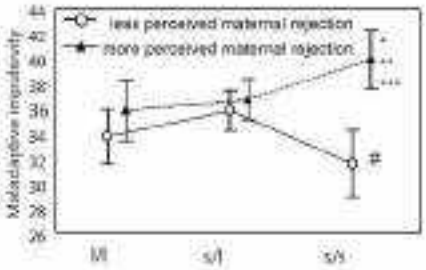
Weber et al. ENPP 2015

NOS1 × Environment on impulsivity



Estonian Children Personality Behaviour and Health Study (ECPBHS)

N=453 18 y.o. Estonian adolescents



- Main effects: males with an s allele had higher score of **Adaptive impulsivity** (**Fast decision-making** and **Excitement seeking**) (p= 0.007).
- Males with the s/s genotype made more errors in the Visual Comparision Test (p=0.001)
- Adolescents with the s/s genotype made more omission errors in the Stop-Signal test

→ NOS1 ex1f-VNTR short/short generally is associated with **Adaptive impulsivity** and **behavioral measures** of impulsivity

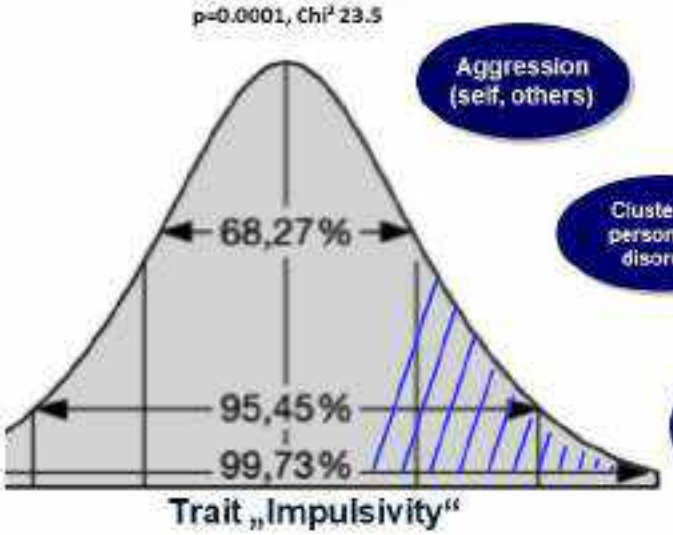
After adversity, *NOS1* short/short is associated with **Maladaptive impulsivity**

Reif et al., Psychopharmacology (2010)

NOS1-Ex1f VNTR is asscociated with impulsivity

Overall psychopathology: p=0.0001, Chi^2 23.5

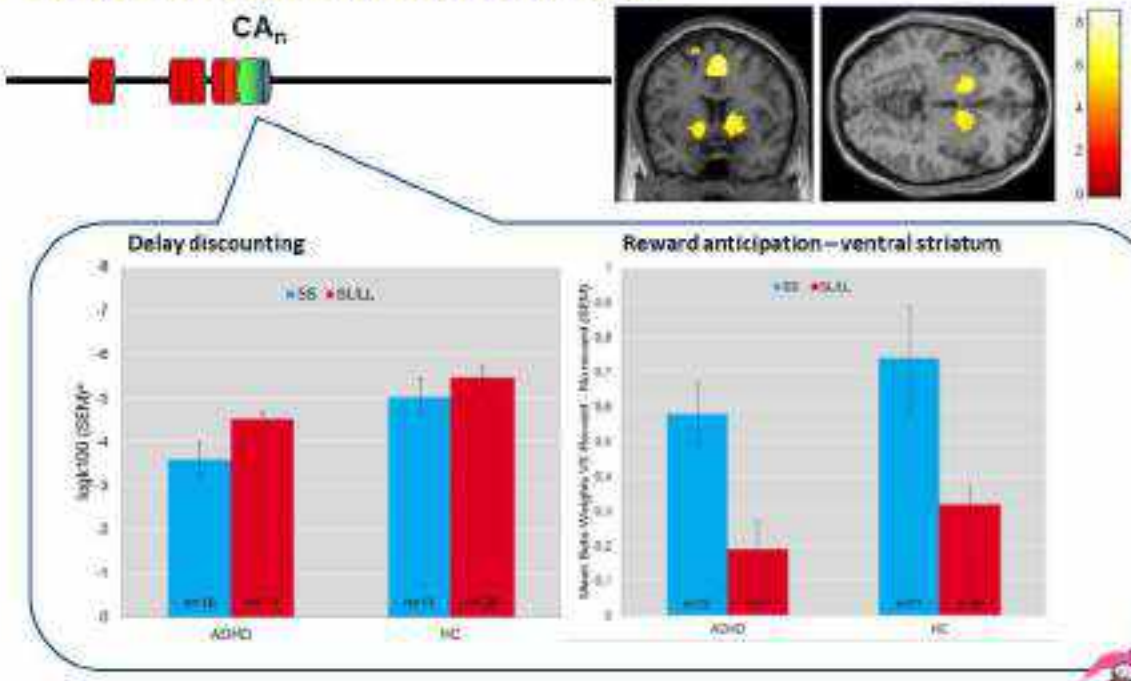
***NOS1* × Environment interaction :** Adaptive → maladaptive impulsivity in the presence of adverse childhood environment



In mice: promotor methylation and *NOS1* expression are changed as a consequence of prenatal environment

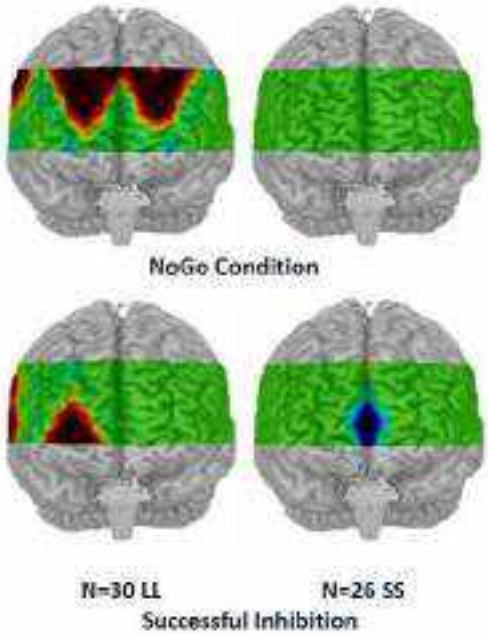
Reif et al. Arch Gen Psychiat 2009; Reif et al., Psychopharmacol 2010; Laas et al., Psychopharmacol 2010; Weber et al., 2014; etc.

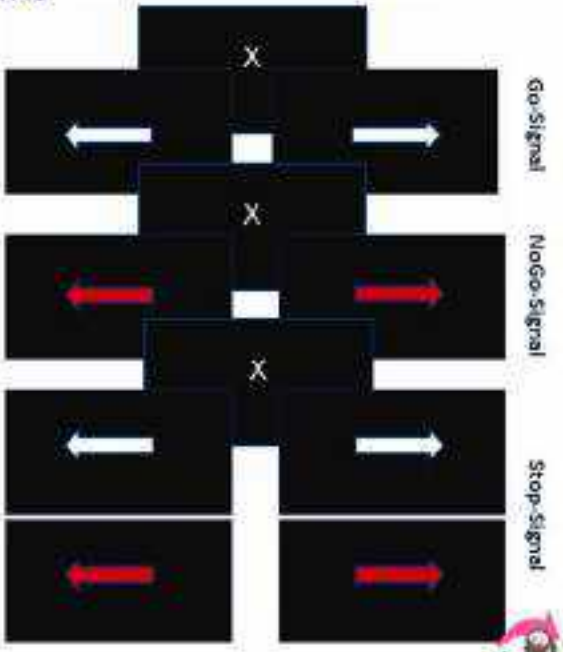
NOS1 and delay discounting



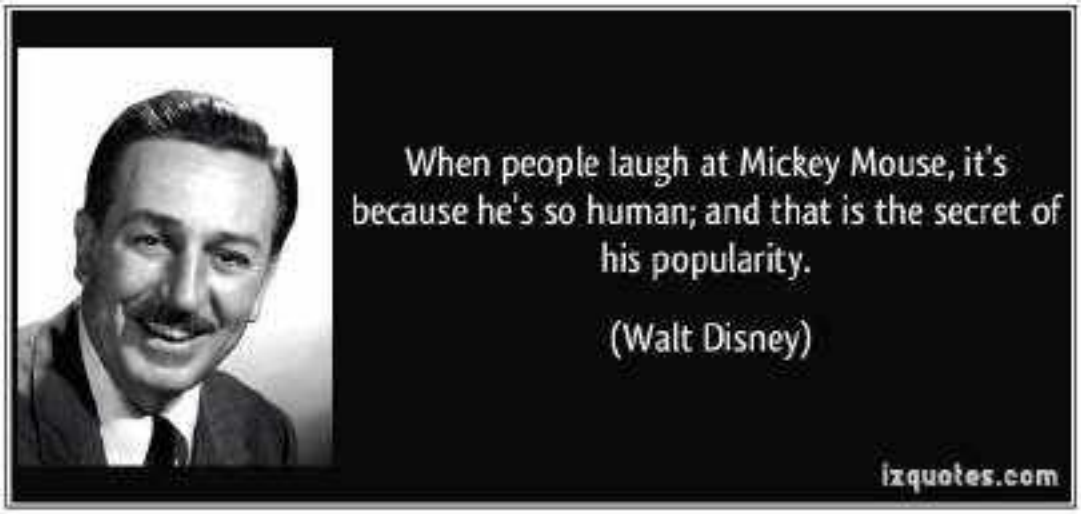
Hoogman et al., Am J Psychiat 2011

Imaging Impulsivity:
GoNogo-/Stop-Signal Test and fNIRS

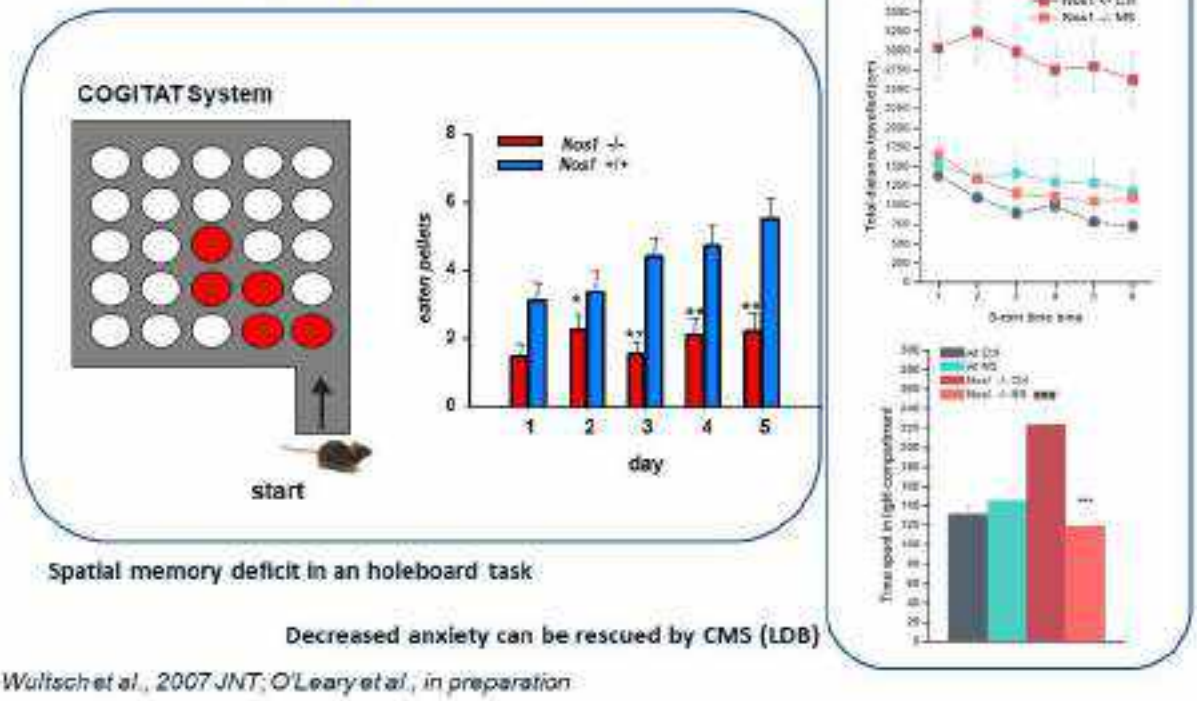




Kopf, ..., Reif, Human Brain Mapping 2012



Nos1 knockdown mice are cognitively impaired and slightly less anxious

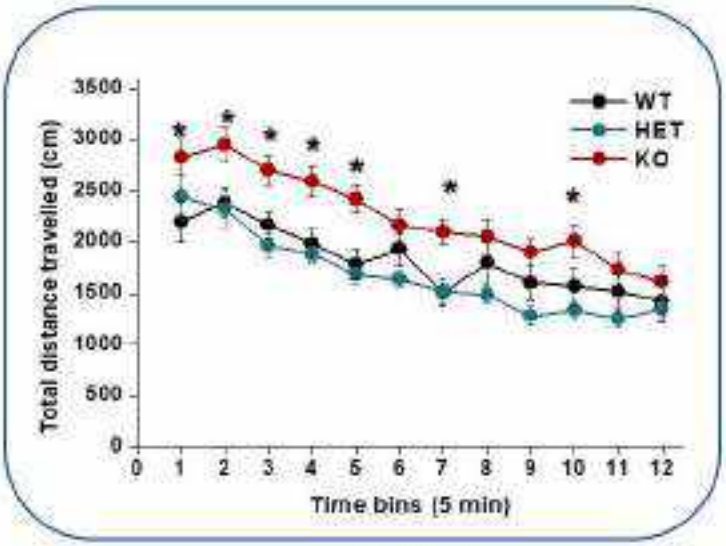


Spatial memory deficit in an holeboard task

Decreased anxiety can be rescued by CMS (LDB)

Wultsch et al., 2007 JNT; O'Leary et al., in preparation

Nos1 knockdown mice are hyperactive



60-min open field test reveals increased locomotor activity in *Nos1* knockout mice

Supported by other studies (e.g. Gao & Heldt, Behav Neurosci 2015)

Nos1 knockdown:

- Aggression (lit.) ↑
- Activity ↑
- Anxiety ↓
- Cognition ↓

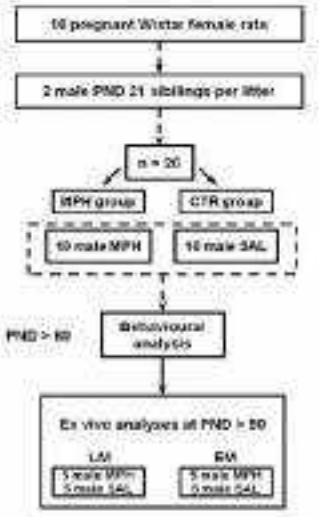
ADHD:

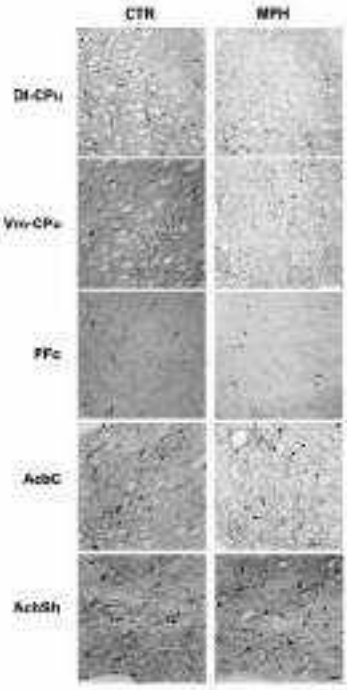
- Impulsivity ↑
- Activity ↑
- Sensation seeking
- Attention deficit, disorganisation

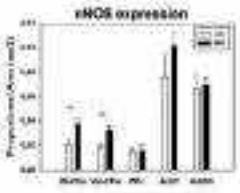
***Nos1 kd* mice as animal models for ADHD?**

O'Leary et al., in preparation

Methylphenidate increases *Nos1* expression

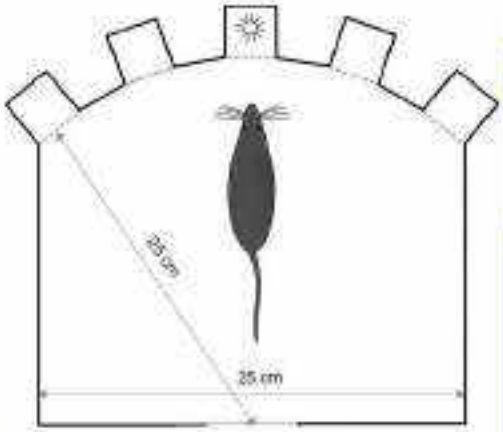






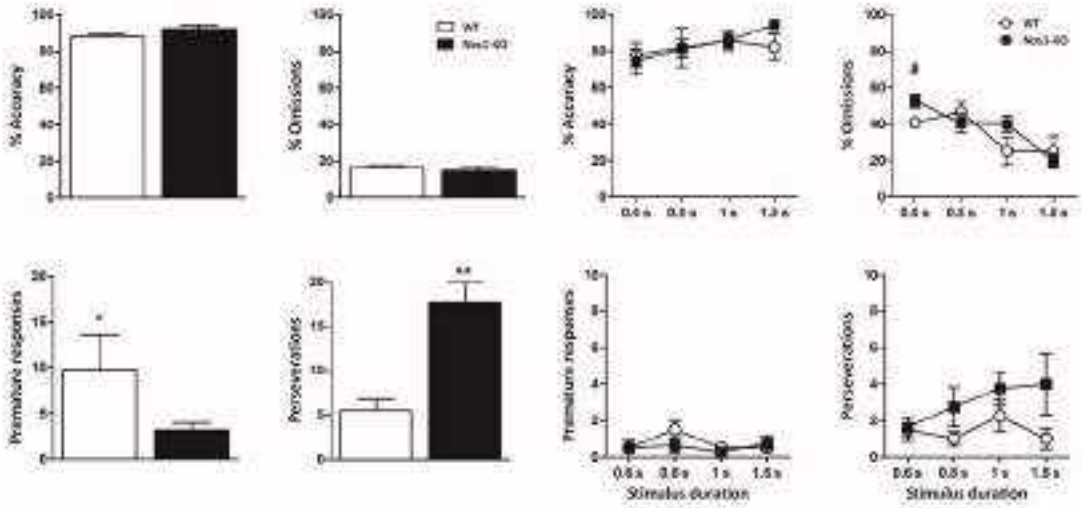
Cavalliere et al., 2012 Eur J NPP

Testing impulsivity in rodents: the 5-choice serial reaction time task (5-CSRTT)



- Decreased stimulus duration increases attentional load and decreases responding accuracy – sustained attention/vigilance
- Prolonged inter-trial interval increases premature responses – behavioural inhibition/impulse control

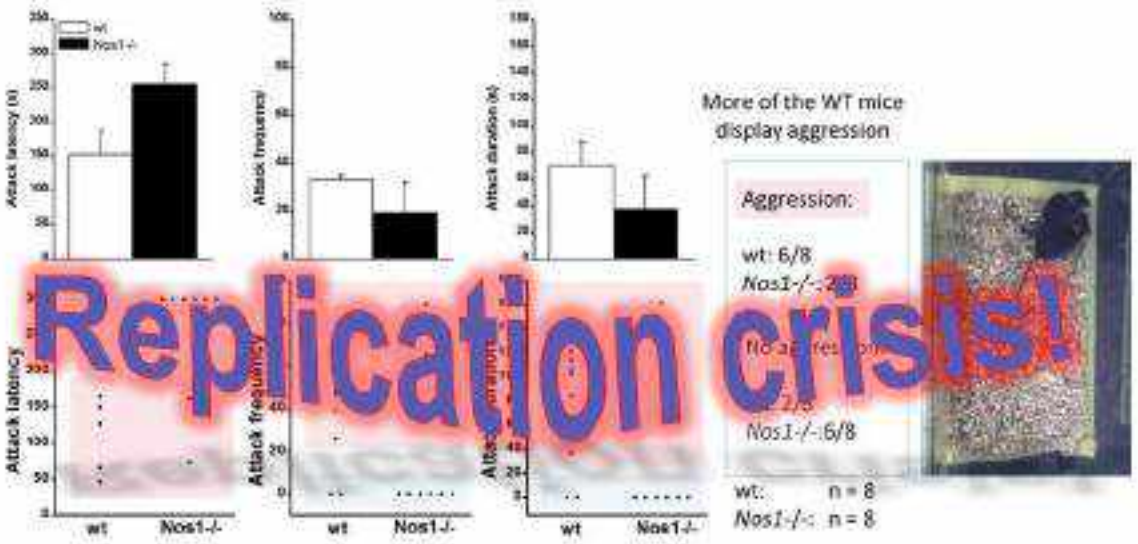
Robbins, 2002



- In the 5-CSRTT, task acquisition, and baseline accuracy and omission rates are normal in the Nos1-ko. They make fewer premature responses and commit more perseverations
  → increased compulsive rather than impulsive behaviour? Cognitive rigidity?
- Nos1-KO mice have a tendency to inattention at very short stimulus durations

O'Leary et al., In preparation

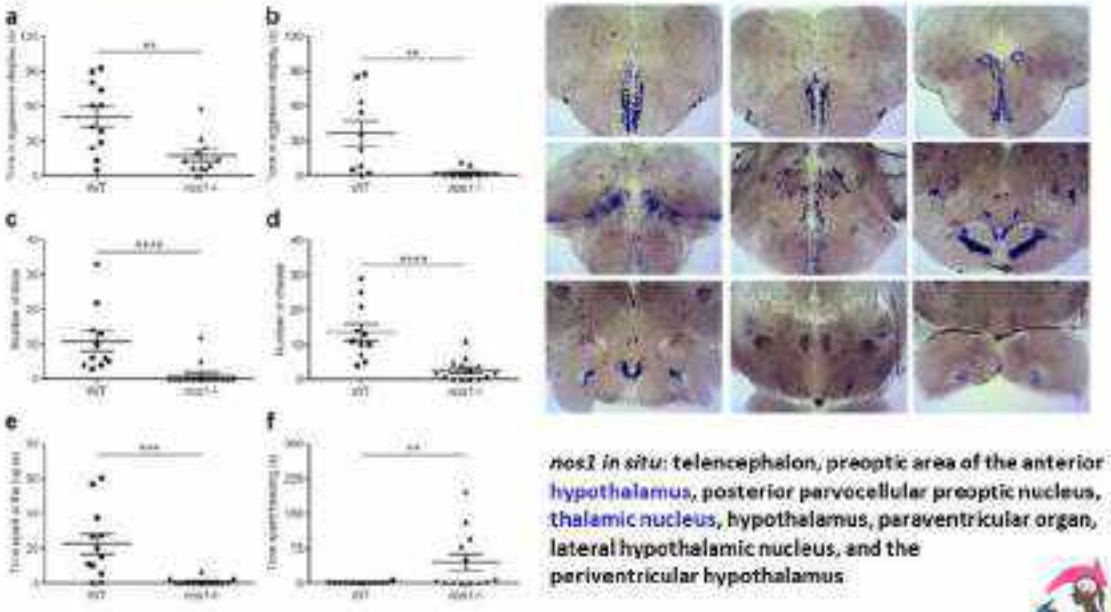
Nos1-kd mice display reduced aggression



Replication crisis!

Carreno Gutierrez et al., submitted to ENPP

Nos1-TALEN mutant zebrafish display reduced aggression

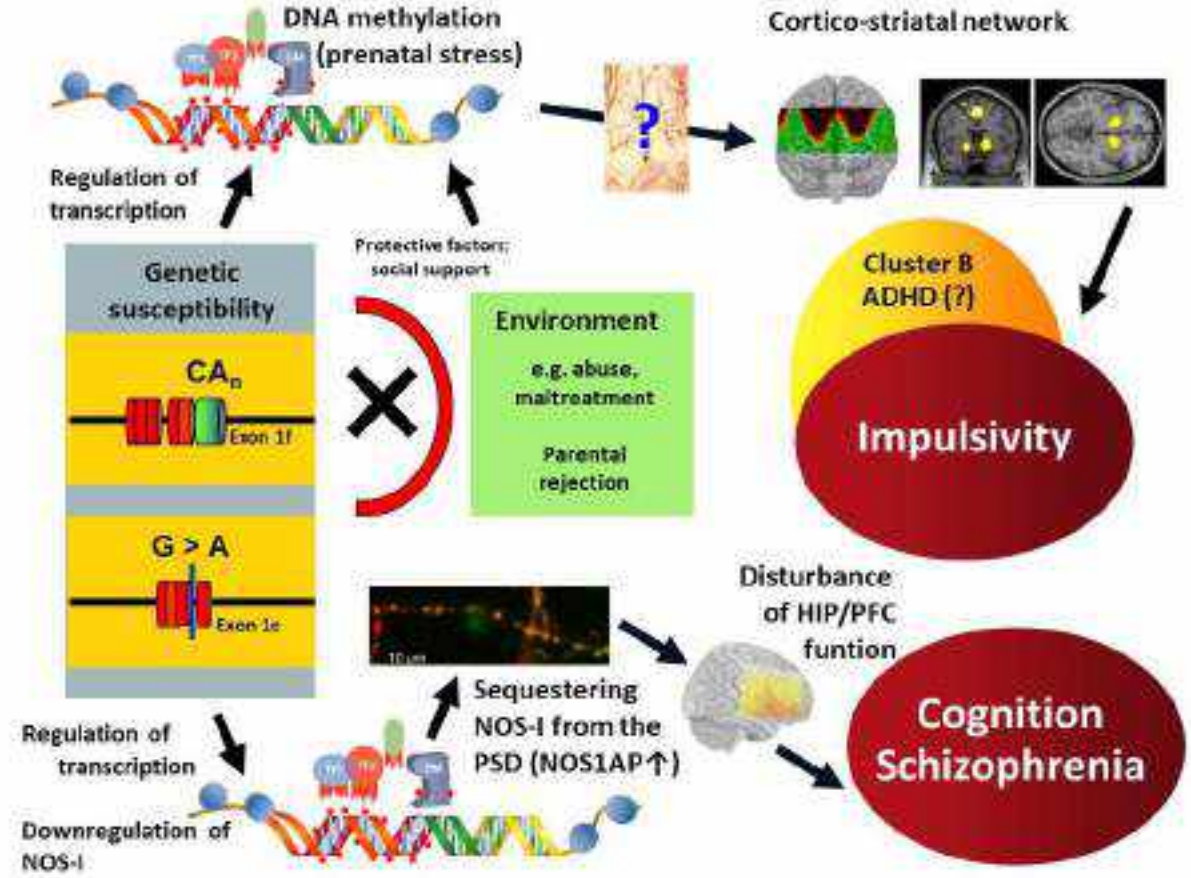


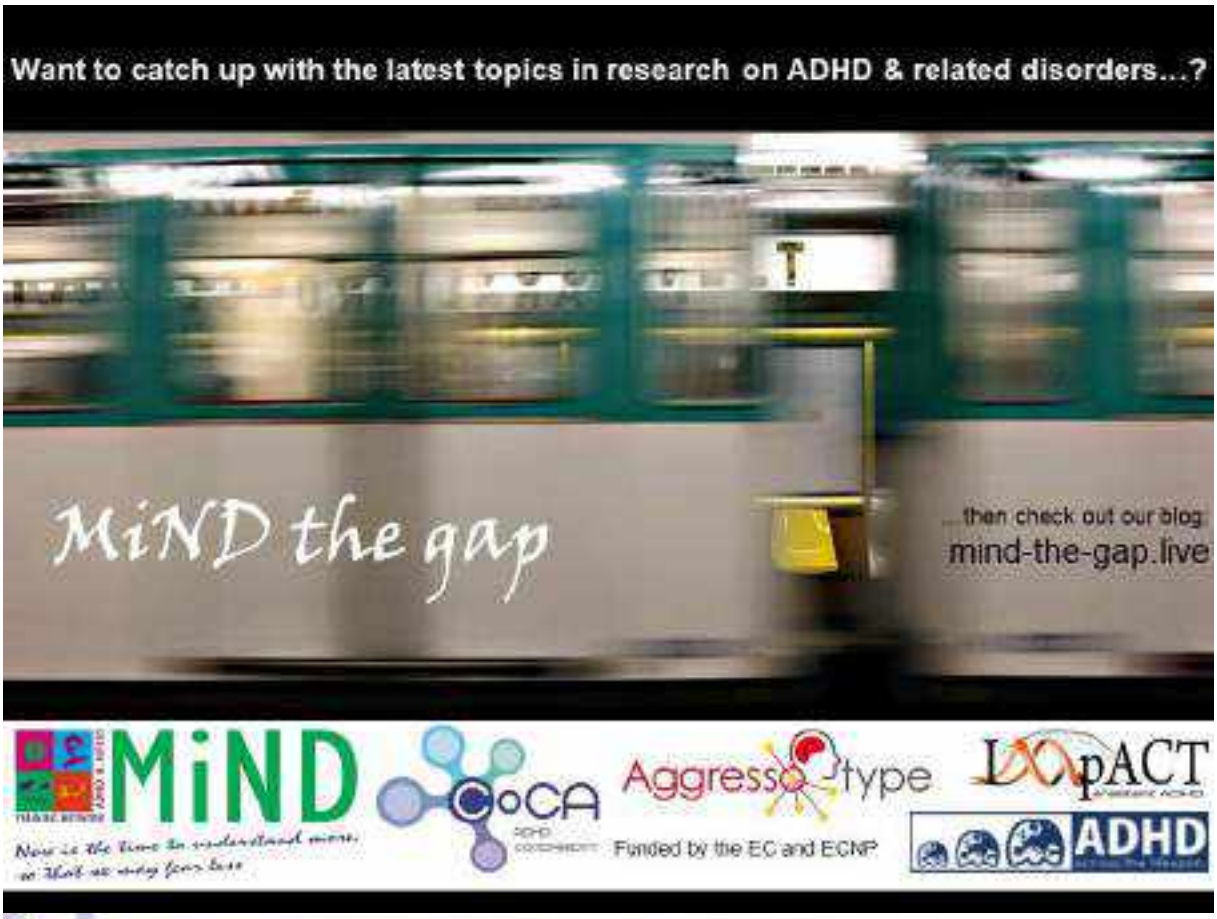
***nos1 in situ*: telencephalon, preoptic area of the anterior hypothalamus, posterior parvocellular preoptic nucleus, thalamic nucleus, hypothalamus, paraventricular organ, lateral hypothalamic nucleus, and the periventricular hypothalamus**

Carreno Gutierrez et al., submitted to ENPP

Conclusions (II)

- Compromised prefrontal *NOS1* function: working memory deficits
  Schizophrenia (esp. human data)
- Compromised hippocampal *NOS1* function: PPI, WM, social interaction: schizophrenia (esp. mouse data)
- Supported by human genetic data
- Reduced *NOS1* expression in the striatum: impulsivity (adaptive vs. mal-adaptive)
  ADHD and other disorders of motor (?) impulsivity
  Compulsivity?





Acknowledgements

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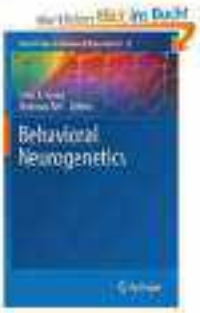

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Aggressotype
MiND
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WIM VAN DEN BRINK

ADDICTION RESEARCH AS A MODEL FOR RESEARCH PLAN AND DESIGN

The case of Heroin Assisted Treatment

Worldwide, opioid dependence is a serious psychiatric problem associated with severe personal suffering, high morbidity and mortality and substantial societal costs. Currently, there is an opioid epidemic in North America with about 60.000 opioid overdose deaths in 2017. i.e. about 200 opioid overdose deaths every day! Fortunately, the opioid situation in Europe is less dramatic, but vigilance is required (Van Amsterdam et al., 2015).

According to data available at the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), Lithuania (1.916.284 inhabitants) has 7.503 high-risk opioid users (4/1.000), about 100 opioid overdose deaths per year (5.6/100.000) and about 55 newly reported HIV-positive cases linked to injecting each year (28.7/million). With these rates, Lithuania has an average prevalence of high-risk opioid users compared to the rest of Europe (1-6/1.00), but a relatively high rate of overdose deaths compared to Europe (2/100.000) and a very high rate of i.v. drug use related HIV conversions (1-2/million). The high rates og negative consequences in Lithuania are paralleled by a relatively low level of opioid agonist treatment in Lithuania: 16% versus 48% in the rest of Europe (EMCDDA, 2018).

In this presentation, I will provide a summary of our work on opioid agonist and related treatments for patients with opioid dependence in The Netherlands. First a brief summary is provided for the effects of methadone maintenance treatment (MMT) until the late 1990s. It is concluded that despite the free access of MMT, about 60% of the treated population shows incomplete response. Therefore, supervised heroin assisted treatment (HAT) for MMT refractory opioid dependent patients was introduced and evaluated. HAT was shown to be effective and cost-effective from a societal perspective (van den Brink et al., 2003; Dijkgraaf et al., 2005). However, many of the patients in HAT continued their comorbid cocaine use with negative consequence for treatment retention and social integration. Therefore, two different interventions were evaluated to reduce cocaine use in these HAT patients: (1) add-on contingency management and (2) add-on sustained release (SR) dexamphetamine. Both add-on interventions were effective (Blanken et al., 2016; Nuijten et al., 2016). A new study is planned to investigate whether add-on SR dexamphetamine is also effective in MMT patients with comorbid cocaine dependence.

The emphasis in this presentation will be on questions about design, study population, primary and secondary treatment outcomes, clinical relevance and statistical power, and generalisation.

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Disclosure

Interest	Name of organization
Grants	Alkermes
Honoraria	Lundbeck, Merck Serono, Eli Lilly, Indivior, Pfizer,
Advisory Board/Consultant	Lundbeck, Merck Serono, Indivior, Mundipharma, D&A Pharma, Bioproject, Novartis, Kinnov Therapeutics, Opiant Pharmaceuticals, Takeda

Tabel of Content

Table of content

- Opioid addiction in Lithuania
- History MMT
- HAT for treatment resistant MMT patients
- Adding cocaine contingency management
- Adding SR Dexamphetamine treatment
- Conclusions and Recommendations

Opioid Situation in Lithuania

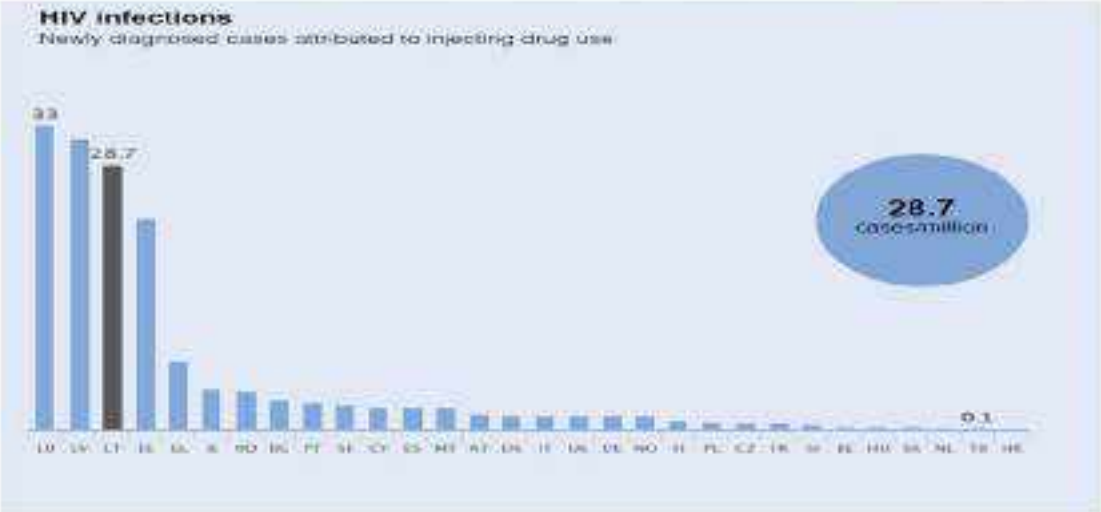
High-risk opioid use in Europe (2007-2015)
Moderately high in Lithuania

High-risk opioid use **stable** at a low rate of 0.1-0.6% of the population

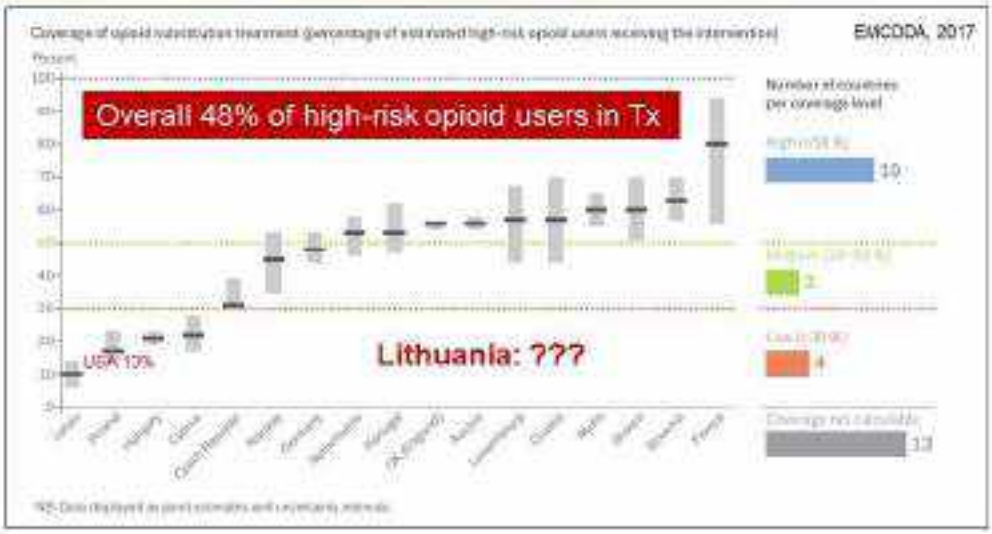
Drug overdose deaths/million) in EU countries
Relatively high in Lithuania: 4/100.000

Overall drug overdose rate is stable between 2000 and 2016 at 2 per 100.000
High and increasing rates in Northern countries: Estonia, Sweden, Norway

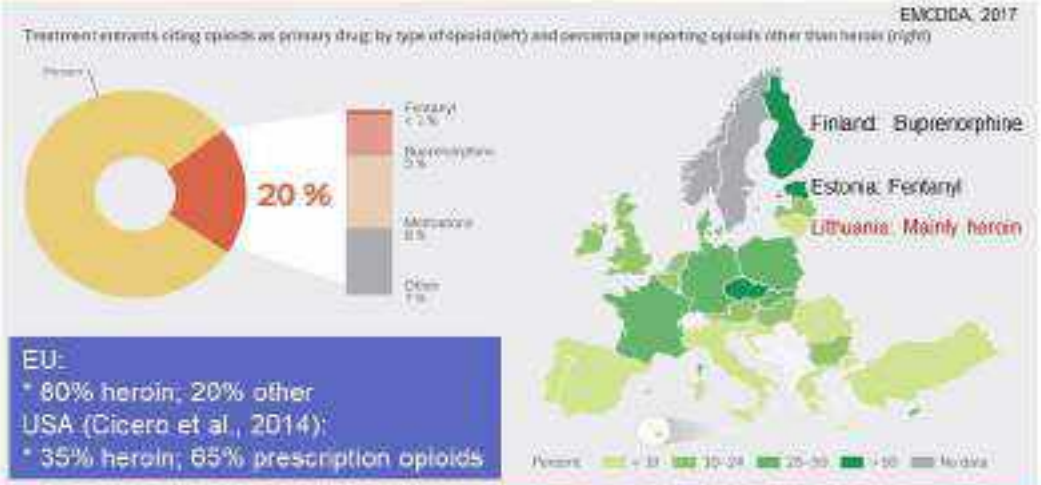
New HIV infections very high in Lithuania



Coverage opioid agonist Tx in Europe
Lithuania: ??



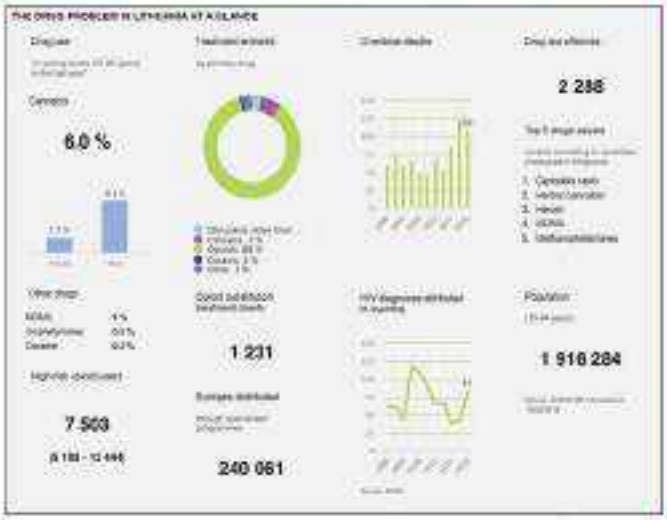
Primary substance of abuse in opioid treatment
Lithuania: mainly heroin



EU:
* 80% heroin; 20% other
USA (Cicero et al., 2014):
* 35% heroin; 65% prescription opioids

In EU (and Lithuania) most opioid dependent Txx still for heroin dependent patients

Drug and Drug Treatment Situation in Lithuania



Population N=1.916.284

High-risk opioid users N=7.503

Prevalence rate = 0.4%

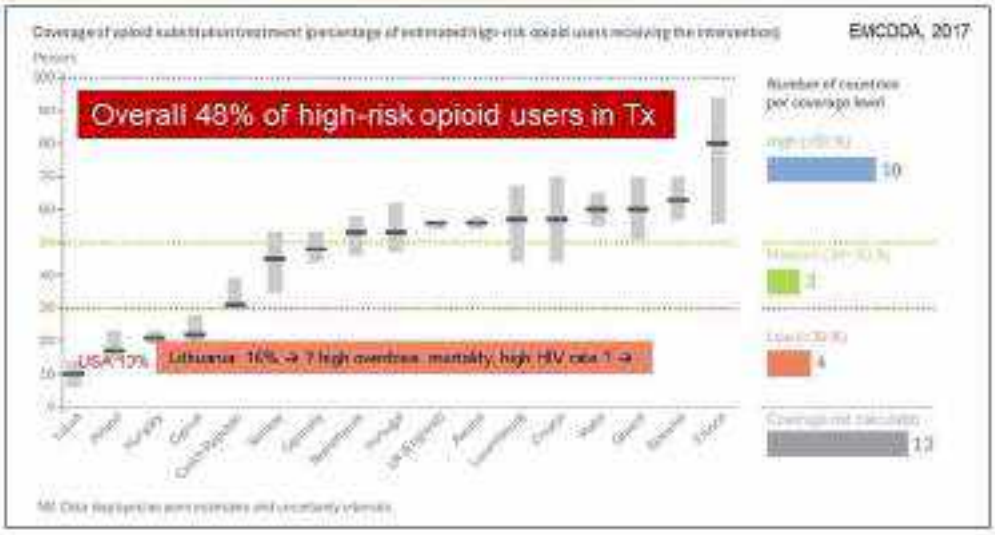
Opiate agonist treatment N=1.231

Substitution coverage = 16.4%

→

HAT probably not needed yet, first fully implement MMT/BMT

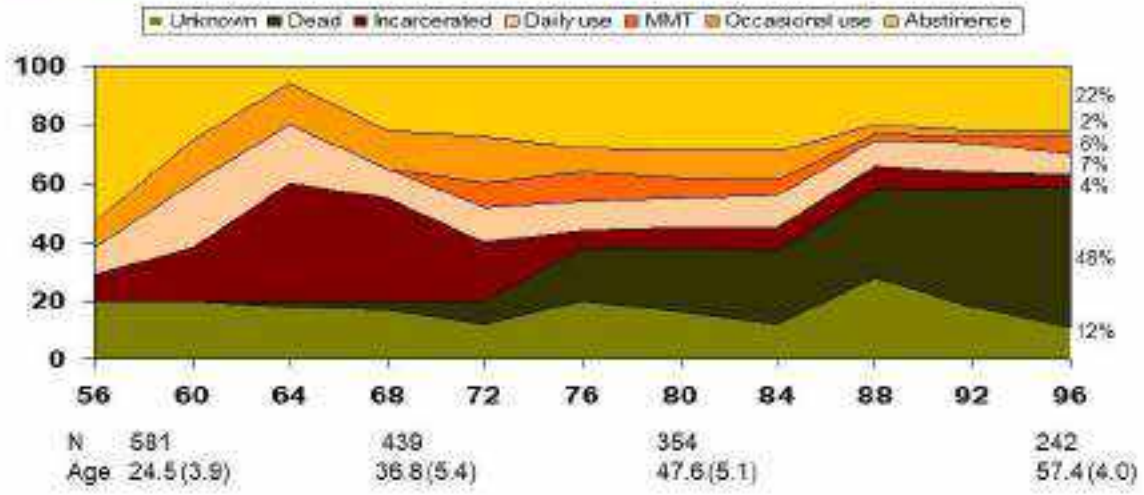
Maintenance treatment opioid dependent patients



History MMT

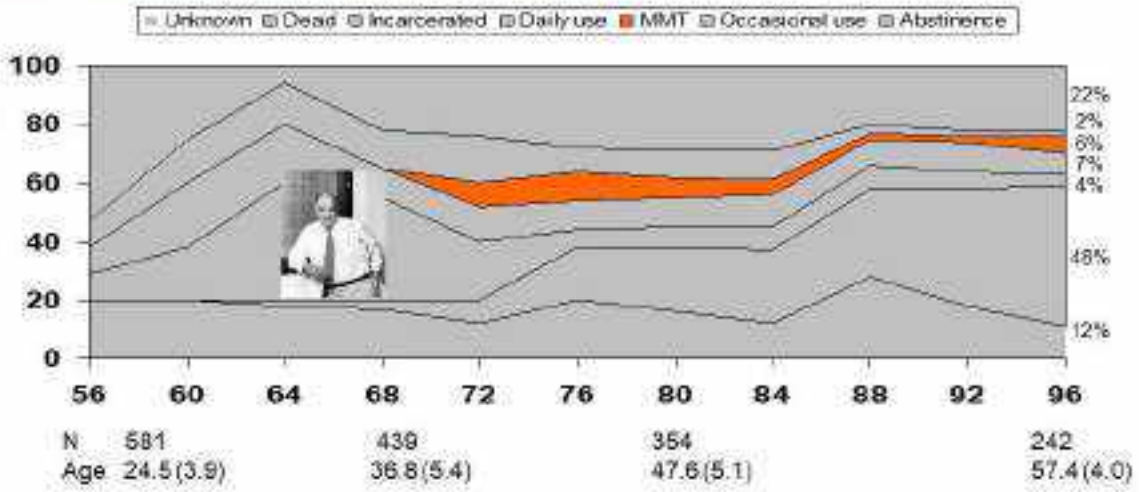
Course of heroin dependence 1956-1996

(Hser et al. 2001)



Course of heroin dependence 1956-1996

(Hser et al. 2001)



Remaining Problems: Zürich Switzerland 1994

Public nuisance despite available and accessible MMT

US experience

UK experience

First Supervised HAT study: Switzerland 1994-2000

Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study

Summary

Cohort study (n=1969)

Positive effects on illicit heroin use and psychosocial outcomes

BUT

* Observational study
* No control group
* Obligatory psychosocial Tx

No causality proven →

Heroin Assisted Treatment in The Netherlands

Open Drug Scenes in The Netherlands (1980s-1990s)

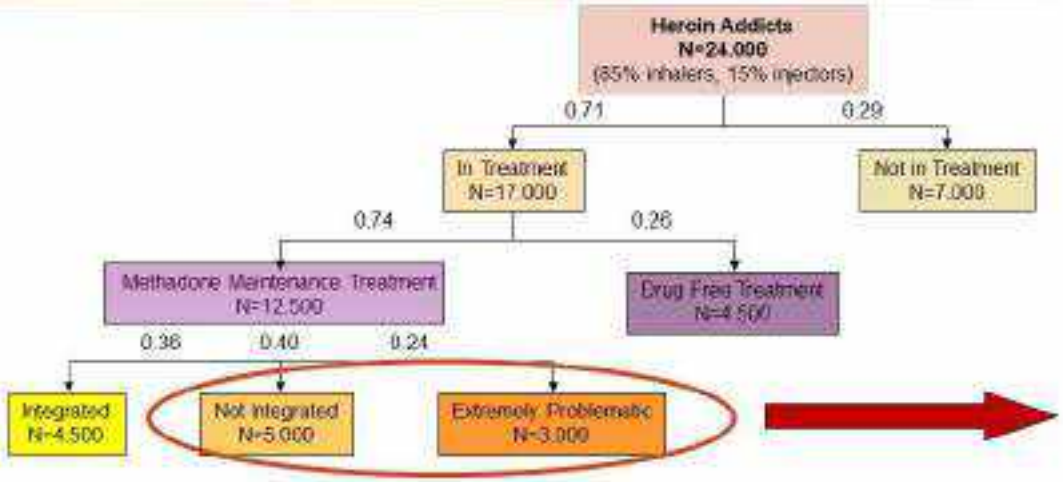
Despite accessible and freely available MMT

Amsterdam, Zeedijk

Rotterdam, Perron 0

Utrecht, Tunnel HC

Netherlands Health Council 1995



Netherlands Health Council 1995

- Continuation existing programmes
  * *drugfree, methadone reduction, and methadon maintenance programs*
- Improving liaison between legal and treatment system
  * *diversion, drugfree prison programs*

Experiment Ultrarapid detox with/without anesthesia

- Experiment High dosage methadone maintenance
- **Experiment controlled heroin-assisted treatment (HAT)**

Questions

(1) Given prior knowledge on HAT, what kind of study design is needed?

(2) Given the type of intervention, what kind of (primary) outcome should be used?

(3) Given the costs of HAT, which additional question should be answered?

HAT in the Netherlands

Two RCTs 1998-2002

Test HAT in chronic, treatment-refractory heroin dependent patients recruited form methadone maintenance treatments

Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials

Wim van den Brink, Vincent M Hendriks, Peter Blanken, Maarten W J Koeter, Barbara J van Zwieten, Jan M van Ree

BMJ

2003 (WoS: May 2017: cited 160 times)

Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials

Wim van den Brink, Vincent M Hendriks, Peter Blanken, Maarten W J Koeter, Barbara J van Zwieten, Jan M van Ree

BMJ

2003

Age (mean)	39 years	
Gender (% males)	81%	
Ethnicity (% Dutch/Western)	66%	
Duration heroin use (mean)	16 years	26 days/month
Duration cocaine use (mean) – 92%	10 years	18 days/month
Duration poly drug use (mean)	17 years	29 days/month
Duration methadone treatment (mean)	12 years	29 days/month
Physical problems (MAP-HSS >8)	66%	
Mental problems (SCL-90 > 41/60)	60%	
Social problems (> 6 days crime/no contact)	72%	

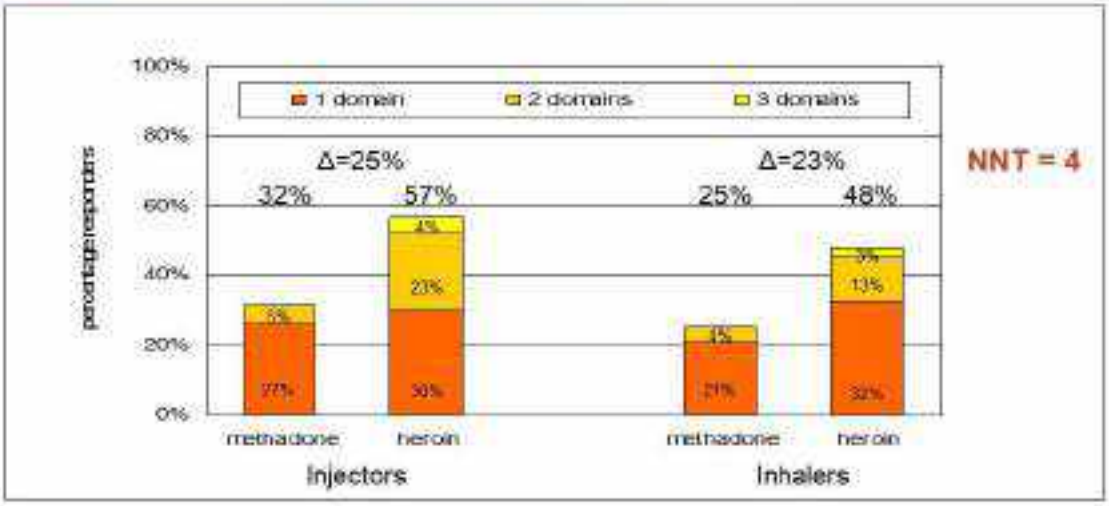
Primary Outcome: Responder

At least 40% improvement in mental health
AND/OR
At least 40% improvement in physical health
AND/OR
At least 40% improvement in social function (incl. criminality)

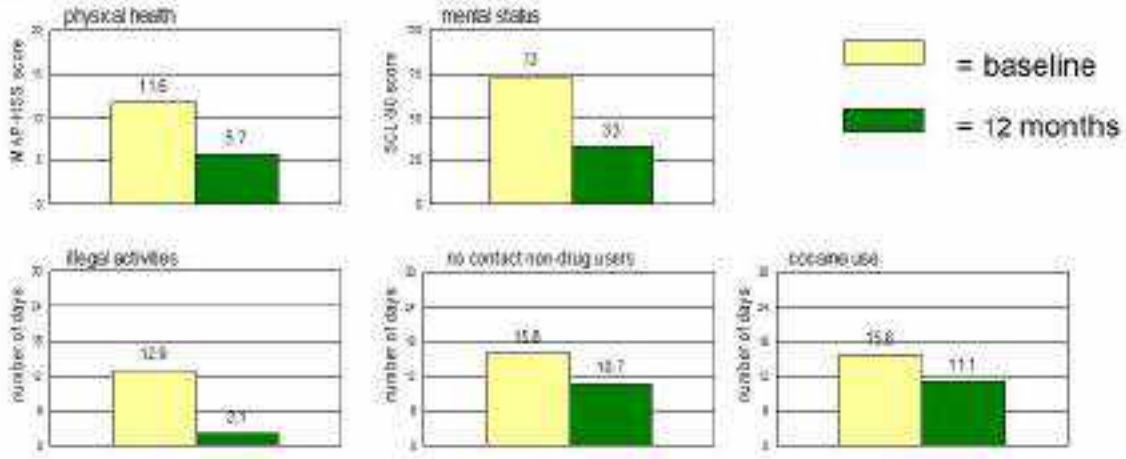
AND
No substantial (>40%) deterioration in any of other domains

AND
No substantial (> 6days/month) increase in cocaine/amphetamine use

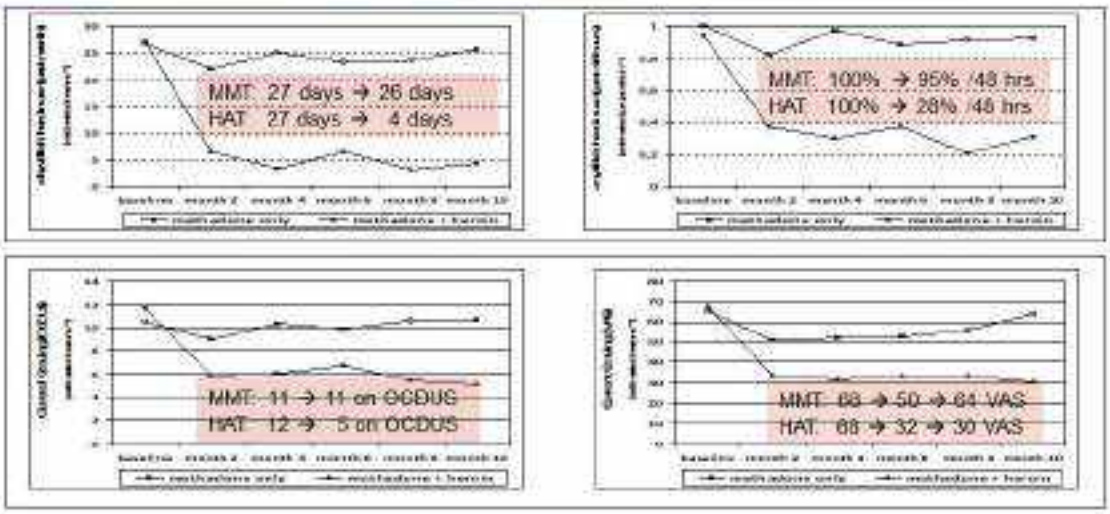
Results: Percentage Responders



Results: Improvement in Responders



Results: Illicit heroin use and craving



Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials

2006

BMJ

Type of Costs		M+H	Difference	M
Medical	Maintenance	€ 18.234	€ 16.982	€ 1.252
	Other Health Care	€ 1.160	€ 34	€ 1.126
Juridical	Police, prosecution, jail	€ 8.756	€ 4.129	€ 12.885
Damage	Victims: persons, companies	€ 9.617	€ 25.374	€ 34.991
Total		€ 37.767		€ 50.560
Difference			€ 12.793	

Efficacy and Safety of HAT

Results of 8 RCTs in 7 countries in 2 continents

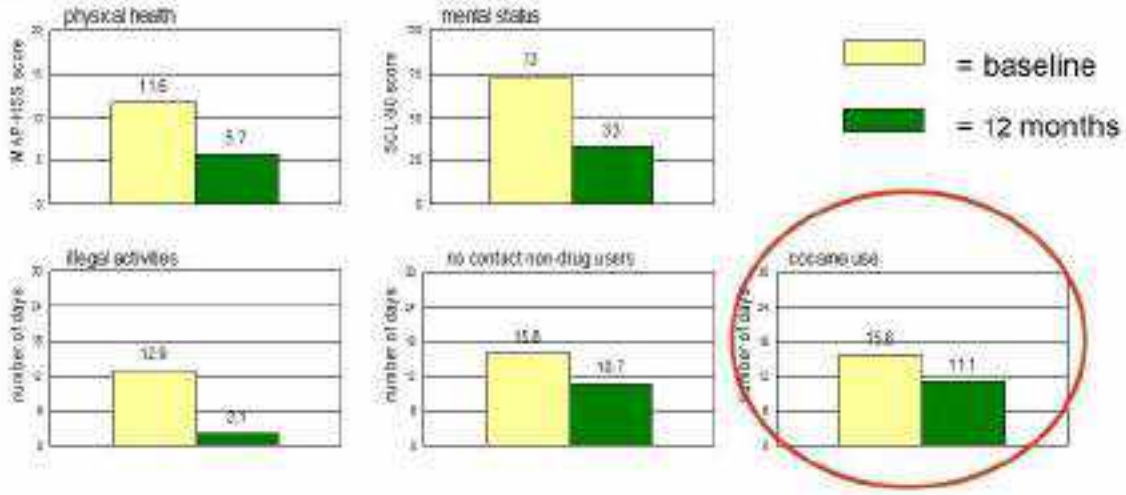
AUTHORS' CONCLUSIONS:

The available evidence suggests an added value of heroin prescribed alongside flexible doses of methadone for long-term, treatment refractory, opioid users to reach:

* a decrease in use of illicit substances, and dcrease in involvement in criminal activity/incarceration,
* a possible reduction in mortality, and
* an increase in retention in treatment.

Due to the higher rate of serious adverse events, heroin prescription should remain a treatment for people who are currently or have in the past failed maintenance treatment, and it should be provided in clinical settings where proper follow-up is ensured.

HOWEVER……..



Questions

**(1) Given this situation,
what kind of intervention is needed?**

**(2) Given the problem,
which population should be studied?**

**(3) Given the type of intervention,
what kind of (primary) outcome should be used?**

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Rationale

- Heroin-assisted treatment is effective,

But

- Only modest reductions cocaine use:
  - at baseline: 84% cocaine use 16 days/month
  - after 12 months: 79% cocaine use 11 days/month
- Cocaine use is predictor of (early) treatment discontinuation

Possible Solutions:

- *add on* interventions to reduce cocaine use
  - * psychotherapy: best choice probably contingency management (CM)
  - * pharmacotherapy: best choice probably SR-dexamphetamine

HAT with *add-on* Cocaine Contingency Management

HAT with add-on cocaine contingency management

Drug and Alcohol Dependence

Full length article

Efficacy of cocaine contingency management in heroin-assisted treatment: Results of a randomized controlled trial

2016

Study objectives

Design

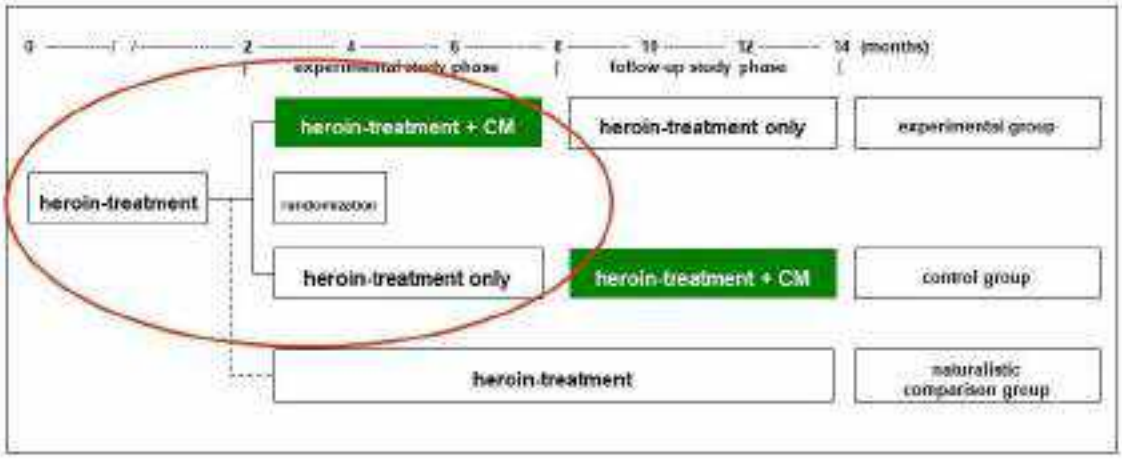
- RCT testing efficacy of 6 months ongoing HAT plus cocaine CM vs. 6 months ongoing HAT alone

Outcomes

- Reduction of cocaine consumption
- Improvements in physical, mental and social health
- Improvements in treatment retention/treatment outcome
- Effect of terminating CM while continuing HAT

Study design

Randomized waiting list design (multi-centre)



Target population

- chronic treatment-refractory heroin addicts
- HAT for two months
- still clinically relevant cocaine use
  - in month before heroin assisted treatment:
    ≥ 1 cocaine positive urine (out of 4), and
    ≥ 4 days self-reported cocaine use; and
  - in second month of heroin assisted treatment:
    ≥ 2 cocaine positive urines (out of 12), and
    ≥ 4 days self-reported cocaine use

LIST OF PARTICIPANTS

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2	Bagdonaitė	Eglė	Kaunas	Lithuania
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14	Kievišienė	Justina	Šiauliai	Lithuania
15	Kiziela	Antanas	Vilnius	Lithuania
16	Kuzmickaitė	Jūratė	Kaunas	Lithuania
17	Laurinaitis	Rokas	Kaunas	Lithuania
18	Liutkevičius	Jonas	Kaunas	Lithuania
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22	Muranovaitė	Rūta	Klaipėda	Lithuania
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24	Narmontas	Gintautas	Vilnius	Lithuania
25	Narmontienė	Neringa	Vilnius	Lithuania
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27	Pakutkaitė	Indrė Kotryna	Vilnius	Lithuania
28	Petraitytė	Karolina	Kaunas	Lithuania
29	Rybakova	Ina	Kaunas	Lithuania
30	Sakalauskaitė	Tautvilė	Kaunas	Lithuania
31	Šalčiūnaitė	Laura	Kaunas	Lithuania
32	Tamošaitytė	Viktorija	Kaunas	Lithuania
33	Užupytė	Austėja	Kaunas	Lithuania
34	Viltrakytė	Ieva	Vilnius	Lithuania

ABSTRACTS OF PARTICIPANTS

Algirdas Musneckis

Sexual Function and Alcohol Consumption Peculiarities of Healthy Lithuanian Males. Biological Psychiatry and Psychopharmacology 2018 Dec;20(2):52-56

Introduction. Male sexual dysfunction is associated with alcohol consumption properties. In some studies moderate alcohol intake was associated with lower risk of erectile dysfunction, reduced sexual fears and promoted sexual desire.
The aim: to evaluate the relations among alcohol consumption habits of healthy Lithuanian males and their current sexual function.
Methods. The research was conducted online using sociodemographic questionnaire, the AUDIT-C test and EMAS sexual functioning questionnaire. The sample size was 285 males.
Conclusions. Despite the fact that Lithuanian males are prone to overdose liquors they are content with their sexual health. Our study did not prove any connection between alcohol consumption and male sexual functioning.

Alicja Juškienė

Type D personality in coronary artery disease (CAD) patients with and without obstructive sleep apnea (OSA).

The aim of the study was to test whether serum levels of thyroid hormones are associated with Thyrotropin, free triiodothyronine, and free thyroxine concentrations were measured in the blood of 494 CAD patients (78 % men), mean age 57.9±9.3. Obstructive sleep apnea (OSA) was assessed by an overnight polysomnography. Personality traits were assessed using Type D Personality Scale (DS-14).
Results showed that Type D personality, both, negative affectivity and social inhibition traits were associated with higher TSH serum concentrations only in women without OSA.

Antanas Kiziela

Double-blinded placebo-controlled evaluation of low doses of Quetiapine efficacy in the treatment of comorbid insomnia

Introduction: The gold standard of treatment for insomnia is CBT-I however, this intervention may not be available in every hospital due to financial or geographical reasons. Quetiapine is widely used in the treatment of insomnia while robust medical evidence of its efficacy is lacking. Moreover, quetiapine has notable side effects (sedation, weight gain, metabolic effects), all things considered, it is important to evaluate harms and benefits of this treatment and if needed, look for better pharmaceutical alternatives.
Aim: Evaluate objective and subjective measures of sleep in the control and experimental group.

Austeja Oganauskaite

Case report: patient with Juvenile Huntington disease (HD)

A 17-year-old adolescent with Juvenile Huntington disease (HD) was hospitalized. At the age of 10, the earliest diagnosis' manifestations (vocal and motor tics) occurred. Later, cognitive impairment manifested. At the age of 15, HD was genetically confirmed by finding of a cytosine-adenine-guanine (CAG) trinucleotide expansion of (n=52-/+3) repeats in the HTT gene. Patient's depression and suicidal ideation's treatment (with sertraline) and tics' correction (with tiapride) was ineffective, neurological symptoms (rigidity, ataxia) occurred. Aripiprazole (for manifested irritability, agitation, apathy and anxiety) had no positive effect. Delusions of exposure and persecution, hearing and visual hallucinations developed. Currently, predominant psychotic symptoms do not correlate with motor symptoms (chorea is absent) and poorly respond to treatment with olanzapine.

Austėja Užupytė

Physical activity addiction: symptoms, epidemiology and comorbidity

The topic of the study that I am planning to start is "Physical activity addiction: symptoms, epidemiology and comorbidity". Exercise and sports activity may have a negative impact on a physical and psychological health if it becomes excessive. My aim of a study is to assess the prevalence of exercise dependance among clients of the fitness clubs of Kaunas city and to examine disorders co-ocurring with exercise addiction such as eating disorders, other types of addictions as well as personality traits which I will measure using different types of the psychometrically valid scales.

Edgaras Diržius

SSRI drugs effect on the Müller-Lyer illusion manifestation for patients with schizophrenia spectrum disorders

Aim of this study was to investigate SSRI effect on the Müller-Lyer illusion (MLI) manifestation for patients with schizophrenia spectrum disorders (SSD). The stimuli were white MLI figures displayed according to Brentano pattern in a black background presented in display. There were 10 experiments carried out with 40 different figures. Position of central figures changed randomly. 40 people were included in the study. Out of 400 experiments performed, during 50 patients were using SSRI. When comparing groups, significant differences were found for 26 of 40 MLI figures.
Conclusion: the MLI tended to manifest stronger for patients who received SSRI.

Eglė Bagdonaitė

The preventive and risk factors for developing cognitive impairment among medical workers in Lithuania

Background. With the increasing of the life expectancy, the average age of practising medical workers in Lithuania has reached 49 years, and still the tendency towards life expectancy is continuing to increase. Therefore, cognitively healthy aging has been prioritised in Lithuania.
Objective. To evaluate the incidence of preventive and risk factors for developing cognitive impairment/ dementia among medical workers in Lithuania, and to predict this risk over a 20-year period.
Materials and methods: In total, 138 medical workers aged 50 years and older (89.9% were females) at three different medical institutions in Lithuania, participated in the cross-sectional study and filled in a
questionnaire developed by authors. The risk for developing cognitive impairment/dementia in 20 years was calculated using the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score.
Results. The one third of subjects (31.2%) had two risk-increasing factors. All subjects had one preventive factor – education and the majority (42.0%) had two additional preventive factors. The risk of 1% for developing cognitive impairment/dementia in 20 years was estimated for 61.6%, 1.9% risk for 34.1% and 4.2% risk for 4.3% medical workers.
Conclusions. The risk of developing cognitive impairment/dementia in 20 years of lifetime among medical workers in Lithuania did not exceed 4.2%.

Gintautas Narmontas

Case report

It is a case from outpatient clinic. 17-year-old male, complaining with difficulties concentrating, excessive sleepiness, high levels of anxiety, obsessive thoughts (fear of losing or not having things you might need, order and symmetry, superstitions, of harm to family members), compulsions and rituals. During further consultations vocal and motor tics were observed. Patient's compulsions intermingle with tics, it is difficult to tell which is which. Treatment with CBT and sertraline was initiated and titrated to 150 mg/d. Observed drug treatment effect was low-moderate. Side effects were observed (anxiety, panic attacks, blunted affect, drowsiness). Sertraline dosage was lowered and risperidone was added. There were no further panic attacks, anxiety level was reduced (but is still well above normal levels), blunted affect disappeared, effect to obsessive thoughts and compulsions was moderate but there we no apparent effect on tics (at this point patient complained about them more than O&C).
Difficulties I encountered:

- Blurred line between compulsions and tics
- Tic treatment remained unsatisfactory
- Adverse effects of SSRI at higher dosage limits their use for obsessive thoughts/compulsions
- Excessive sleepiness got a bit better with sleep hygiene but remains a problem

Ieva Viltrakytė

Clinical cases: insomnia

In my daily outpatient clinical work, I usually face difficulties when treating sleep disorders, because patients prefer to combine pleasant falling asleep together with long-lasting treatment and low possibility of tolerance/addiction. I feel lack of knowledge in this field, would like to have a discussion and share cases with my colleagues and teachers of ECNP Neuropsychopharmacology Seminar.
Participating in the Seminar, I would like to present a series of clinical cases when my patients had poor sleep even with separate additional treatment (antipsychotics, sleep-inducing antidepressants) for insomnia together with underlying treatment for main anxiety or affective disorders.

Ina Rybakova

The role of alcohol consumption in suicide attempt risk

Introduction. The rate of committed suicides is decreasing vaguely and remains quite high in Lithuania. Evidence based suicidal behavior studies are most relevant in seeking effective suicide prevention.
Research goal and methods. To define suicidal behavior properties of those who attempted suicide using questionnaire that includes sociodemographic and suicide attempt characteristics, CAGE questionnaire.
Results. There were 637 participants, mean age 38.59±14.05 years, 56.99 % were problem drinkers; 73.37 % of males and 51.05% of females used alcohol prior suicide attempt.
Conclusions. Hazardous alcohol consumption is related to increased suicide attempt risk.

Indrė Kotryna Pakutkaitė

Depression among patients with Huntington's disease (HD)

Higher rates of depression among Huntington's disease (HD) gene carriers
Study involved 33 individuals referred for genetic testing for HD mutation and 42 individuals from the general population. We assessed depression and anxiety rates for individuals with and without HD mutation before genetic testing and compared them with the general population.
We found that more than a half of individuals with HD mutation were diagnosed with depression. The prevalence of depressive symptoms was higher for individuals with HD mutation than for the general population or for those who undergo HD genetic testing but do not have the mutation. Anxiety symptoms were more common among individuals with HD mutation than those in the general population.

Inga Domskytė

The peculiarities of intelligence in children with autism spectrum disorders

Introduction. IQ has major importance for prognosis and treatment outcomes of autism spectrum disorder (ASD).
Objectives. A group of 55 children with ASD and clinical control group of 26 children without ASD took part in this study.
Results. Both groups involved in the study are homogeneous by age. There was no statistically significant gender difference in the evaluation of intelligence results. Performance IQ ($p<0,026$) and perceptual organization index ($p<0,012$) are higher in ASD group. Comprehension in the ASD group is lower than in the control group ($p=0,028$).

Ingrida Kazlauskaitė

Association between coping styles and adherence to antipsychotic treatment

Objectives: To identify the association between coping styles and adherence to antipsychotic treatment.
Methodology: The study involved 49 inpatients diagnosed with schizophrenia or schizoaffective disorder and 55 individuals in control group. During the interview two questionnaires (Brief COPE, MARS) were administered.
Results. Turning to religion, mental and behavioral disengagement, and substance use as a coping styles were used more frequently comparing to the controls. Clear associations have been established between adherence to antipsychotic therapy and elderly age (OR = 1, 05), and an acceptance as a coping style (OR = 1, 73). The nonadherence was associated with considerably higher rates of substance use (OR = 0, 44).
Conclusions. The patients' attitude towards unpleasant life events and substance use can improve the prediction of their adherence to antipsychotic medication regimens.

Jonas Montvidas

The influence of negative symptoms on the quality of life

The research is still not completed. Aim. To adapt self-report negative symptom scale (SNS) in Lithuania and evaluate the impact of the severity of negative symptoms on the quality of life (QoL). Method. We will use SNS and BPRS to evaluate negative symptoms and SF-36 to evaluate the quality of life of stable inpatient and outpatient participants diagnosed with schizophrenia. Then we will compare the results of SNS and BPRS scales and evaluate the impact of the severity of negative symptoms on the QoL Anticipated outcomes – the SNS is more sensitive when detecting negative symptoms than BPRS and the increase in the negative symptoms' severity is linked to decrease in QoL.

Jonas Liutkevičius

Evaluation of benefits, integrating Cognitive and behavioral psychotherapy mindfulness meditation practice in child and adolescent psychiatry in-patient hospital settings

There is evidence that mindfulness helps develop effective emotion regulation in the brain, enable people to become less reactive, have greater cognitive flexibility, improve relationship satisfaction, enhance functions associated with the middle prefrontal lobe area of the brain, such as self-insight, morality and intuition, and fear modulation.

The aim of study is to understand interest and willingness to practice mindfulness of children and adolescents, diagnosed with affective and anxiety disorders. Target group would get brief mindfulness meditation course in first days of entering hospital and different criteria will be evaluated with control group, such as length of treatment, mood and motivation for treatment improvement and willingness to cooperate with clinicians participating in treatment.

Jonas Fugalis

Organic delusional [schizophrenia like] disorder caused by a primary brain disease

One of the possible reasons – hyperprolactinemia caused by prolactinoma. In most cases prolactinoma simptoms include infertility, headaches, oligomenorrhea or amenorrhea, galactorrhea, very rarely – acute psychosis. When prolactinemia is present and its secondary causes are excluded, diagnostic gold standart is brain MRI with contrast. If the test is unavailable or there are contrindications of doing it, head CT with intravenous contrast can be useful, but is less informative. Initial choice of treatment of hyperprolactinemia should be dopamine agonists – cabergoline, bromocriptine. Safest choice of treatment of psychosis with hyperprolactinemia is aripiprazole, quetiapine may be an alternative. We report the case of a 27-year-old woman with prolactinoma and hyperprolactinemia induced acute psychosis.
Key words: prolactinoma, hyperprolactinemia, acute psychosis.

Julija Dimšaitė

Case report

Introduction: a 41-year-old woman who was intoxicated with alcohol was admitted to the Psychiatry Clinic.
Case description: the patient was episodically disoriented locally, in time and in self, emotions inadequate, thinking was slow and inconsistent, cognitive impairment has been observed. In the unclear state, no treatment was given and the patient was monitored for a while. The patient was treated with Tiapride, but Tiapride had to be discontinued due to changes in ECG. The patient's condition did not change significantly for two weeks. Hypokalaemia, hypocalcaemia, elevated C-reactive protein, vitamin D deficiency have been observed in laboratory tests. No source of infection was found. The patient's condition did not change significantly for two

weeks. Mental condition began to improve with correction of hypocalcaemia and vitamin D interference.

Julija Gečaitė

Associations between sleep quality and cardiovascular response to Trier Socials Stress Test (TSST) in CAD patients

The mechanisms, linking physiological stress reactions and subjective sleep quality (SQ), are still under-explored in CAD population. We aimed to investigate associations between SQ and cardiovascular response (blood pressure and heart rate) to Trier Socials Stress Test (TSST) in CAD patients 2 weeks after acute coronary syndrome. In total, 161 study participants completed TSST and were evaluated for sociodemographic (84% males, age: 53±9), clinical and SQ (PSQI) characteristics. After controlling for gender, age, NYHA functional class, arterial hypertension, depressive symptoms, Type D personality, and use of beta-blockers, worse SQ remained to be linked with higher blood pressure during TSST.

Julius Burkauskas

The association between fatigue and cognitive functioning in patients with anxiety and mood disorders

Fatigue is prevalent in patients with anxiety and mood disorders and might be linked with various disorder-specific cognitive dysfunctions. However, the precise nature of the inter-relationship is poorly understood. In patients with comorbid anxiety and mood disorders (n=113, 77% female; mean age: 38 ± 12 yr) we evaluated the association between fatigue and cognitive functioning, to generate new heuristics for clinical management. We made stringent attempts to control for the potentially confounding effect of relevant socio-demographic and clinical factors. Fatigue was associated with worse cognitive function, particularly psychomotor speed and level of executive interference independently of possible confounders.

Jūratė Kuzmickaitė

Virtual reality technology as the possibility in treating of anorexia nervosa

Virtual reality technology enables the evaluation of pathological eating behaviors and body image distortions it also provides a better sense of presence as well as treatment abilities (virtual work on patients' body image and exposure to virtual food stimuli). Some studies using VR-based environments associated to CBT showed their potential utility in improving motivation for change, self-esteem, body image disturbances. I would like to do a study using Virtual reality technology to explore the possibilities of treating anorexia nervosa by three-dimensional figures of the patient's body to be presented, helping them to reach an awareness of body image, resulting in a more realistic body image and a decrease in body image dissatisfaction.

Justina Kievišienė

Case report: client with addiction

Client with addiction: expression of specialist‘s personality traits during interaction process
Despite the continuing aspirations of the state and various professionals to reduce alcohol dependence the situation is not improving enough. And nowadays almost every health care specialist encounters addiction issues. Scientific literature show that specialists with specific core characteristics and moral or spiritual values may have considerably huge impact for patient’s well-being. This research aims to find what personality becomes the main tool in the effective counseling and treatment of addict to alcohol person. Methodology of research: meta-analysis of two surveys: quantitative (personality trait assesment) and qualitative (in-depth interview). Resting on research results recommendations for bettter specialist self-awareness would be presented.

Karolina Petraitytė

Alcohol use disorder (AUD) treatment with Disulfiram: guaranteed success?

The aim will be to review the effect of Disulfiram in the treatment of outcome patients with AUD in primary care. The effect of disulfiram will be evaluated according to outcomes such as alcohol intake, days until relapse and numbers of drinking days. I want to compare retrospective 2 outcome groups by sociodemographic indicators: first time patients diagnosed with AUD and received treatment with Disulfiram, compared to patients without alcohol-aversive drugs.

Kostas Matuzevičius

Case report: woman with schizoaffective disorder

I would like to present a clinical case of a 58 years old woman with schizoaffective disorder, who experienced a severe treatment resistant depressive episode with psychotic symptoms and developed a delayed onset postictal delirium during the ECT treatment course with major cognitive disturbances. The case was unique and extremely challenging and raises many difficult and yet unanswered questions about the diagnosis and the optimal choice of treatment.

Kristina Butkutė Šliuožienė

The diagnostic peculiarities of a case with epilepsy, cognitive disorder and déjà vu

The diagnostic peculiarities of a case with epilepsy, cognitive disorder and deja vu will be discussed. A 23-year-old male patient was referred to a psychiatric evaluation for suspected psychosis. The patient presented similar to psychosis symptoms – complaint of constant frustrating visual imagery of people, places. He also had seizure episodes, including loss of consciousness and generalized convulsions, in the past. These symptoms appeared after the patient had herpetic encephalitis, while seizures started 3 years before encephalitis. Predominant symptoms in mental condition were anxiety, memory, attention, cognitive function disorders and sensations of images, which patient was very difficult to describe.

Laura Šalčiūnaitė

Theory of Mind (ToM) functioning test in association to chronic pain and personality traits

Objective: To explore whether deficits in Theory of Mind (ToM) functioning test are associated to chronic pain, and whether these are related to patient's personality traits.
Subjects: 60 patients with chronic pain and 60 healthy participants (control), matched for sex, age and educational level.
Methods: to test subjects mentalizing abilities, we are going to use the Frith-Happe´-Animations Task – an established ToM measure, to assess subjects' personality traits – Eyseneck Personality Questionnaire, finally, to evaluate pain – pain perception questionnaire, based on McGill pain questionnaire, pain localization, intensity and duration scales.

Laurynas Ambrasas

Comorbidity of impulsive-compulsive disorder's and Parkinson's disease

Questionnaire's approbation for impulsive-compulsive disorder's and Parkinson's disease comorbidity diagnosis. There is an increase in prevalence of impulsive-compulsive disorders related to dopamine replacement therapy, yet these disorders are frequently overlooked. Most of the time it is influenced by stigmatization, disregard for the problem, i.e. Standardized and approved questionnaire for the patient should help in this regard. The layout of this research consists of these parts: statistical analysis of the comorbidity's diagnosis in Lithuania, its comparison to other countries; projected financial benefit to the healthcare system; questionnaire's design and approbation, recommendation of its implication to outpatient care.

Miglė Kaminskaitė

Association of genetic polymorphism (COMT rs4680, DRD2 rs1800497, SLC6A3 rs27072, ORM1 177791) to alcohol addiction disorder and personality traits,

Research is focused on genetic polymorphism, that might attenuate brain reward system and its modulation (COMT rs4680, DRD2 rs1800497, SLC6A3 rs27072, ORM1 177791). We seek to establish their association to alcohol addiction disorder and association to personality traits, that are characteristic to individuals with addiction disorders. The results of study might be helpful for better understanding of addiction pathogenesis, with respect to endophenotypes and for future development and selection of personalized treatment.

Mindaugas Baranauskas

Th development of new method to cope with addictions based on biofeedback and stimulus presentation for humans.

Representation of psychophysiological state (interoception) and autonomic regulation are interrelated, both are altered in addicted persons. Interoceptive effects of drugs, alcohol, cigarettes represent major controlling process that regulates substance-seeking behavior. Autonomic responses to cues could serve as measure of substance addiction severity and craving. We aim to develop new method to cope with addictions based on biofeedback and stimulus presentation for humans.

Neringa Narmontienė

Case report: female patient with polymorphic symptoms

Patient female, 56 y.o., in-patien clinic. Main complaint – recurring episodes of seeing her son being dead at night (dreamy states?, nightmare?, hysterical symptom?). Patient has 35 years history of epilepsy (temporal lobe, TLE) with polymorphic seizures:

- generalized tonic-clonic seizures;
- short loss of consciousness - things fall, burns hands (atonia? absence?), 5 y.
- focal autonomic / vegetative - abdominal pain, nausea, diarrhea, 3 y.
- focal-affective paroxysm - frequent nightmares, wake up at night, feeling of fear.

Typical dissociative seizures were also observed.
Hysterical as well as organic personality traits were observed.
Main concern – differential diagnosis of patient states and symptoms.

Rokas Laurinaitis

Creating new tools to evaluate patients' satisfaction in primary care

Patient satisfaction improves patients' compliance, adherence to treatment and it is known to improve treatment outcomes. There are no appropriate instruments in Lithuanian language to evaluate patients' satisfaction in primary care.
Aim is to design valid, reliable and easy to use questionnaire to evaluate patients' satisfaction levels in primary care.

Rūta Muranovaitė

Associations between cardiovascular disease risk reduction (measured by heart rate variability [HRV]) and change in depression symptoms

Mindfulness based practice (MBP) might positively influence cardiovascular disease risk via an indirect pathway including change in emotion regulation. A study was conducted in order to investigate associations between cardiovascular disease risk reduction (measured by heart rate variability [HRV]) and change in depression symptoms, before and after 3 weeks of MBP, in patients diagnosed with Somatoform Autonomic Dysfunction of Cardiovascular System. Research demonstrated significantly greater change in depression scores for participants engaged in three weeks of MBP when compared to control group. A significant correlation between HRV and depression symptoms was found only in the treatment group.

Tautvilė Sakalauskaitė

Case report: psychiatry and general medicine meeting points

Psychosomatic medicine has been a specific area of concern within the field of psychiatry for more than 50 years. The practice of psychosomatic medicine has evolved considerably since its early clinical origins and has come to focus on psychiatric illnesses that occur in the setting of physical health care. The primary objective for psychosomatic medicine is the diagnosis and treatment of psychiatric disorders in patients with complex medical conditions. Psychiatric assessment in the medical setting includes a standard psychiatric assessment as well as a particular focus on the medical history and context of physical health care.

Viktorija Tamošaitytė

Case report: anti NMDA receptor encephalitis at children age

A case about 9 years old boy with complicated, diverse differential diagnosis. Usually this disorder is accompanied with various psychiatric symptoms, which leads to delayed determination of diagnosis and treatment. At given case symptoms started as neurological (seizures), and the boy was admitted to Neurological department later as the psychiatric symptoms appeared, he was treated in the psychiatric hospital. Due to worsening condition later on he was transferred to Hospital of Lithuanian University of Health Sciences (LSMU), where after some tests he was diagnosed with NMDA encephalitis. Treatment of psychiatric symptoms was complicated due to specific reaction to neuroleptics and poor symptomic psychiatric treatment guidelines. At the given case benzodiazepines were most effective treating agitation, delirium.

Viltė Malinauskienė

The rates of treatment resistant schizophrenia

We're planning to perform a study investigating rate of treatment resistant schizophrenia (TRS). The aim: assess the prevalence. The tasks- investigate the prevalence; determine: types of medications; attempts' are made to achieve therapeutic doses prior to treatment adjustment; frequency and reasons of antipsychotics change.
Data gathered would carve a path for broader study; assess treatment quality; identify whether TRS's diagnosed early enough. Expected results: If the prevalence doesn't differ significantly from many countries, it'll be 10-30%. Insight would allow: address the need for researches; assess the need for: additional education; implement algorithms in Lithuania, ensuring adequate treatment.