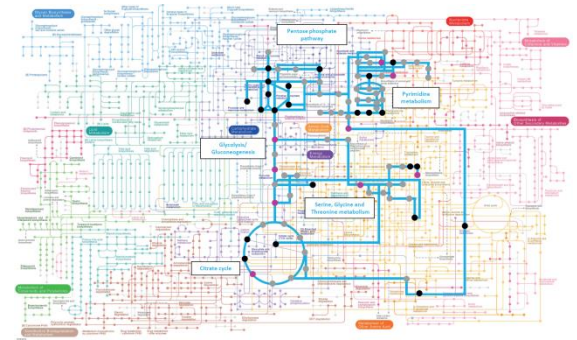
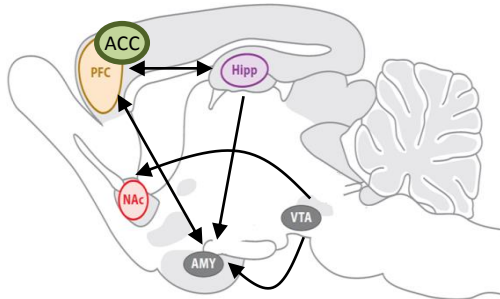
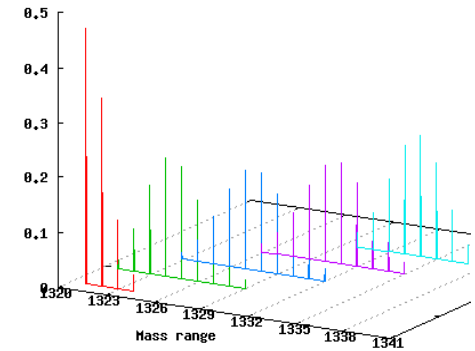
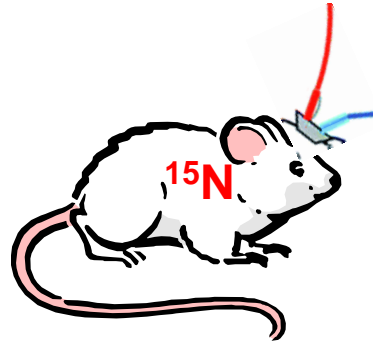
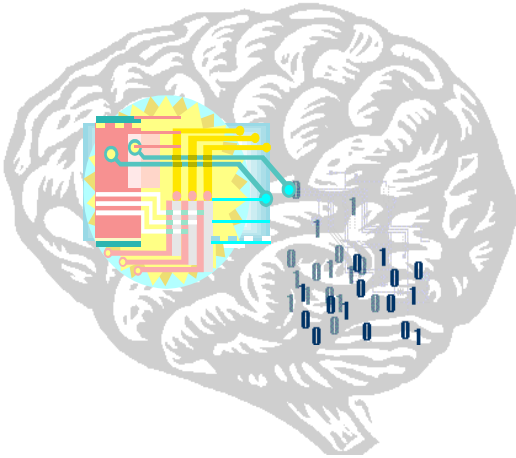




# Biomarkers for Psychiatric Disorders



# From Bench to Bedside and Back ...

## Max Planck Institute of Psychiatry





# Ten leading causes of burden of disease (WHO)

2004 Disease or injury	As % of total DALYs	Rank		Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1		1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2		2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3		3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4		4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5		5	3.8	COPD
Cerebrovascular disease	3.1	6		6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7		7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8		8	2.7	Refractive errors
Road traffic accidents	2.7	9		9	2.5	HIV/AIDS
Neonatal infections and other <sup>a</sup>	2.7	10		10	2.3	Diabetes mellitus
COPD	2.0	13		11	1.9	Neonatal infections and other <sup>a</sup>
Refractive errors	1.8	14		12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15		15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19		18	1.6	Diarrhoeal diseases

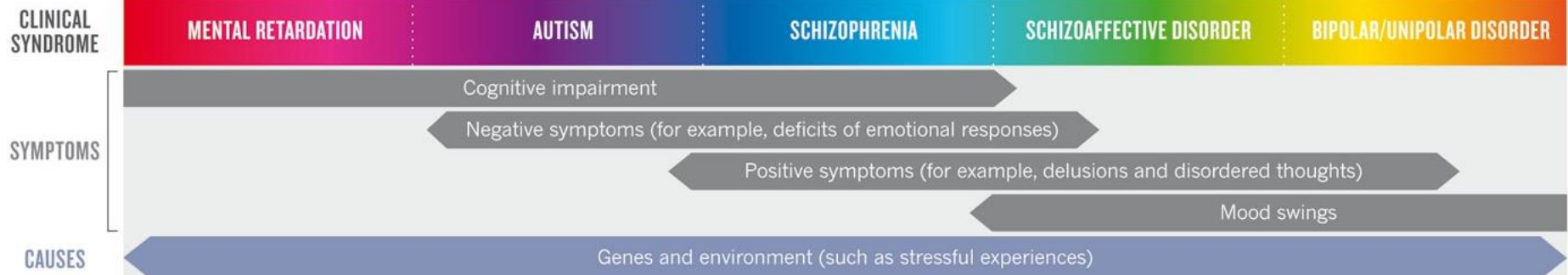
# Problem #1

## Poor Diagnosis - Artificial Disease Classification



**Depression**

**Bipolar Disorder**



*Adam D. Nature 496:416-418 (2013)*

**Anxiety**

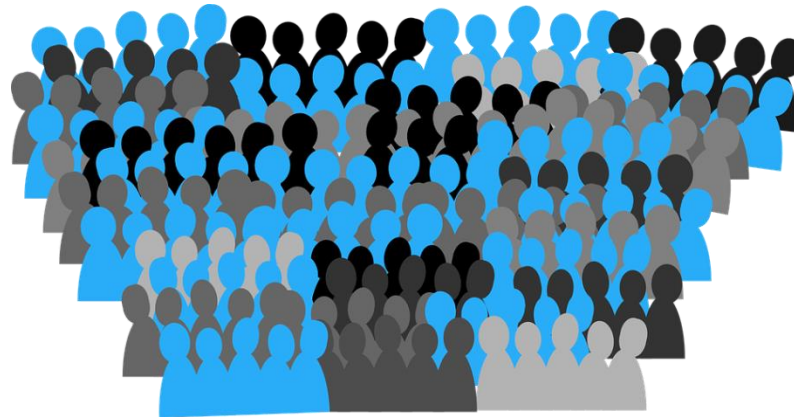
**Schizophrenia**

# Problem #2

## Antidepressant Response – Imprecise/Impersonal Medicine



Good Response



Residual  
Symptoms



No Response

- 2-4 weeks to evaluate response
- switching to alternative antidepressant
  - => prolonged suffering
  - => suicide risk
  - => high healthcare costs







# Top Therapeutic Classes by Prescriptions

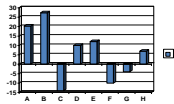
DISPENSED PRESCRIPTIONS MN	2007	2008	2009	2010	2011
Total US Market	3,825	3,866	3,949	3,993	4,024
1 Antidepressants	237	241	247	254	264
2 Lipid Regulators	233	242	254	260	260
3 Narcotic Analgesics	231	239	241	244	238
4 Antidiabetics	165	166	169	172	173
5 Ace Inhibitors (Plain & Combo)	159	163	166	168	164
6 Beta Blockers (Plain & Combo)	162	164	163	162	161
7 Respiratory Agents	147	147	152	153	153
8 Anti-Ulcerants	134	139	146	147	150
9 Diuretics	137	135	132	131	128
10 Anti-Epileptics	102	110	116	122	128
11 Tranquillizers	98	101	104	108	111
12 Thyroid Preparations	103	104	105	107	110
13 Calcium Antagonists (Plain & Combo)	87	90	93	96	98
14 Antirheumatic Non-Steroid	90	91	92	93	97
15 Hormonal Contraceptives	94	94	93	91	90
16 Angiotensin II Inhibitors	83	86	85	84	86
17 Broad Spectrum Penicillins	77	74	77	76	77
18 Macrolides & Similar Type Antibiotics	63	66	69	67	69
19 Hypnotics & Sedatives	58	60	63	63	63
20 Vitamins & Minerals	60	59	58	58	60

IMS Health, National Prescription Audit, Dec 2011

The Use of Medicines in the United States: Review of 2011  
Report by the IMS Institute for Healthcare Informatics

# Biomarkers

Objectively measured characteristic reflecting physiological, pharmacological, disease processes.



## ➤ **Diagnosis**

- follow disease (stationary, relapsing, etc.)
- pre-symptomatic detection

## ➤ **GWAS dataset query**

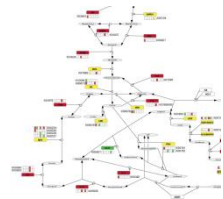
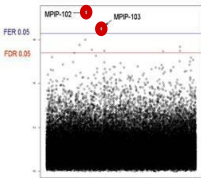
- select a limited list of candidate genes
- tolerate interrogation of genes with higher p-values

## ➤ **Drug development**

- patient stratification
- monitor clinical response to treatment

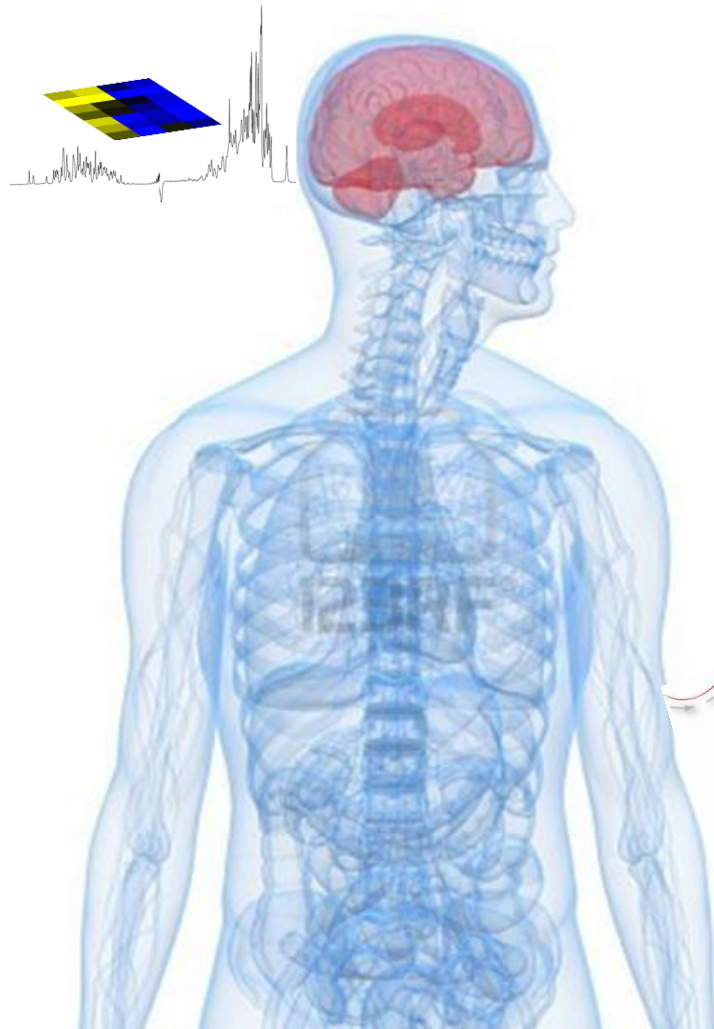
## ➤ **Improved understanding of disease processes**

- pathway analysis
- target dysfunctional pathways instead of mutant genes



# Peripheral vs. Central Biomarkers:

## Do They Correlate?



### ➤ Discovery

- profiling analyses to generate list of biomarkers from relevant tissue (differential expression, turnover, etc.)

### ➤ Qualification

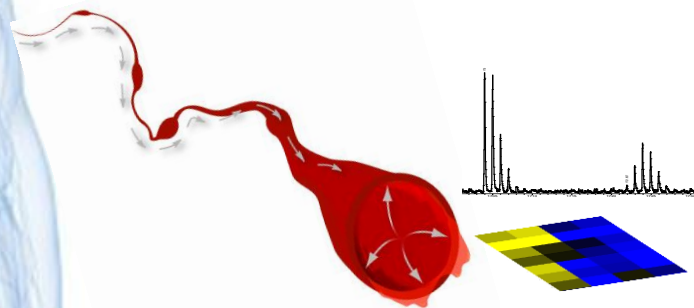
- link with biology

### ➤ Verification

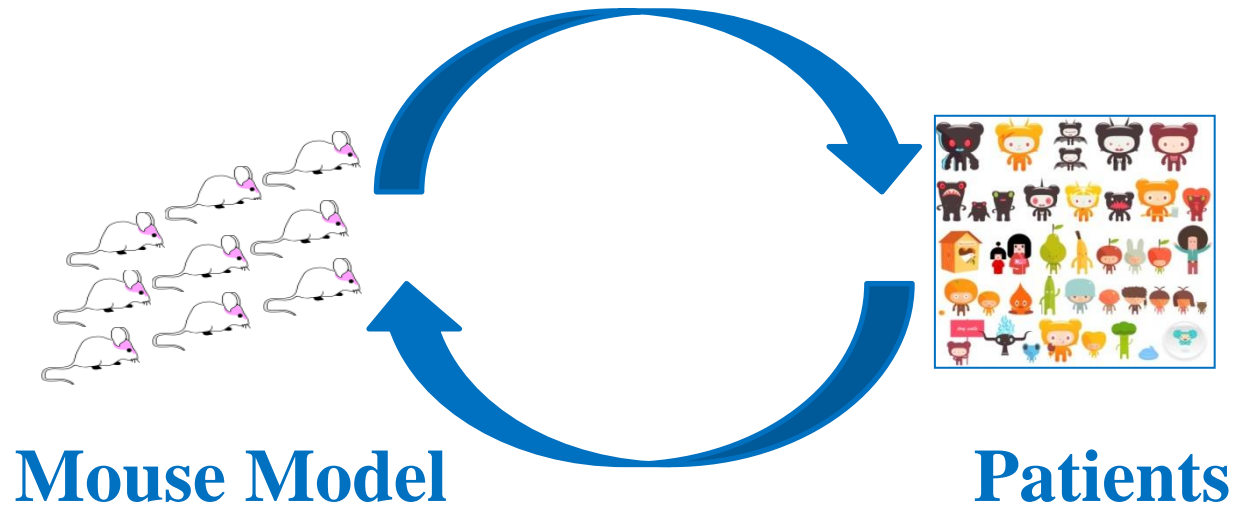
- screen peripheral fluid for presence

### ➤ Clinical validation

- robust, sensitive, specific quantitative method







- **inbred**
- **homogeneous phenotype**
- **controlled environment**
- **primary tissues**

- outbred**
- heterogeneous phenotype**
- variable environment**
- body fluids**
- limited cohorts**



➔ It is not the aim of animal research to mimic the complexity of human nature, but

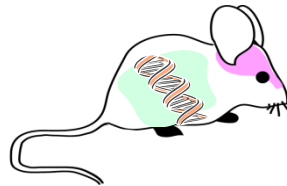
... to model selected endophenotypes (face validity)

... to test for the efficacy of pharmacological compounds (predictive validity)

... to study similarities in cellular and molecular processes (construct validity).

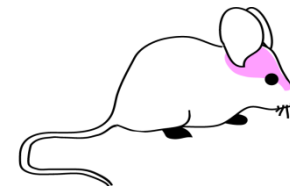


## Genetic Risk Factors



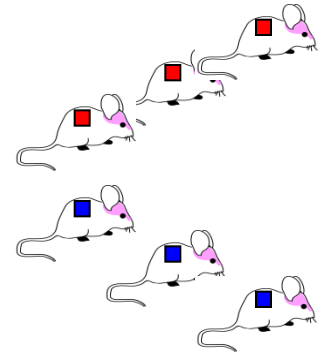
**bottom-up**

**Genetic Manipulation**  
(ko, transgenic)



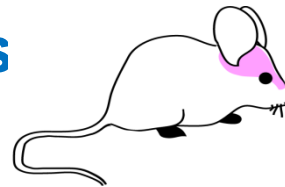
**top-down**

**Selective Breeding**  
(trait)



## Developmental Risk Factors

**Maternal Separation**



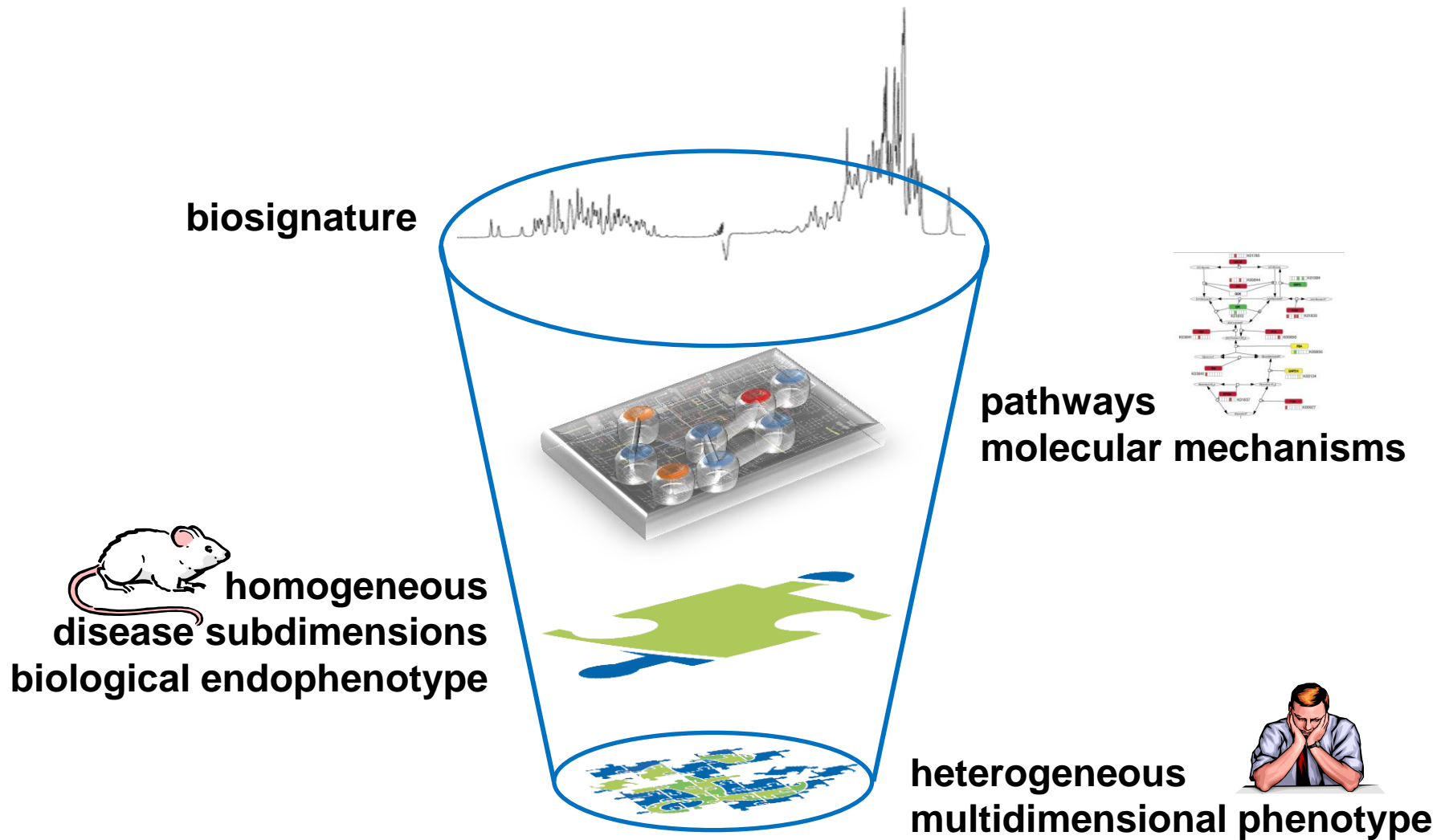
## Aversive Life Events

**Social Stress, Trauma, Repeated Restraint**





# From Phenotype to Biosignature





# Post-Traumatic Stress Disorder

Exaggerated implicit fear memory resulting from

- **associative fear conditioning**
- **non-associative sensitization processes/fear components**



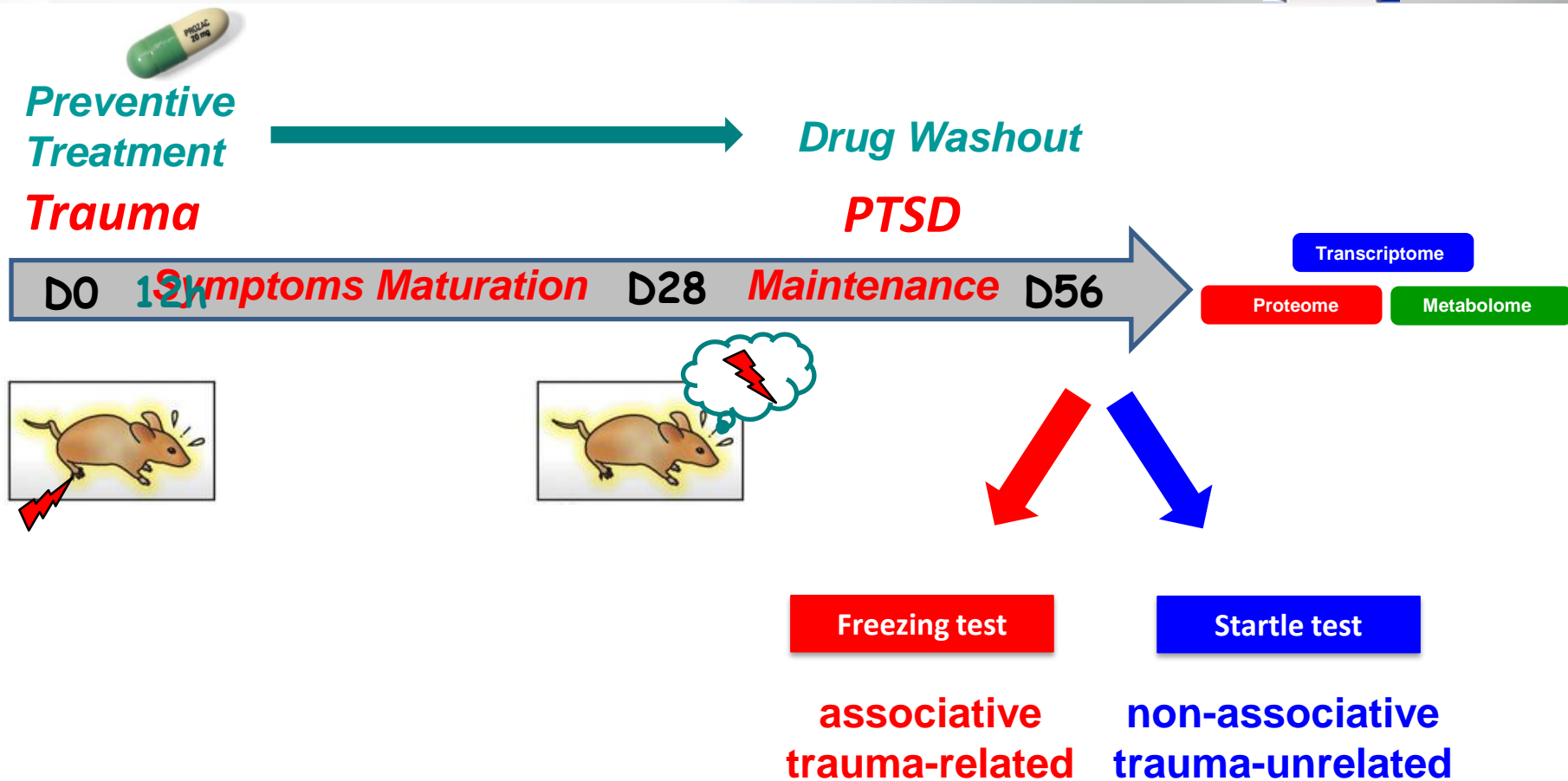
## Symptoms

- **Related to memory of trauma**
  - Re-experiencing
  - Flashbacks
  - Nightmares
  - Avoidance of and exaggerated response to cues reminding of the trauma
- **Unrelated, lack of association**
  - Hyperarousal
  - Hypervigilance
  - Increased startle
  - Blunted emotionality
  - Social withdrawal



# PTSD Mouse Model

## Shock Sensitization and Pharmacological Treatment



Chi-Ya Kao  
Carsten Wotjak  
Philipp Khaitovich

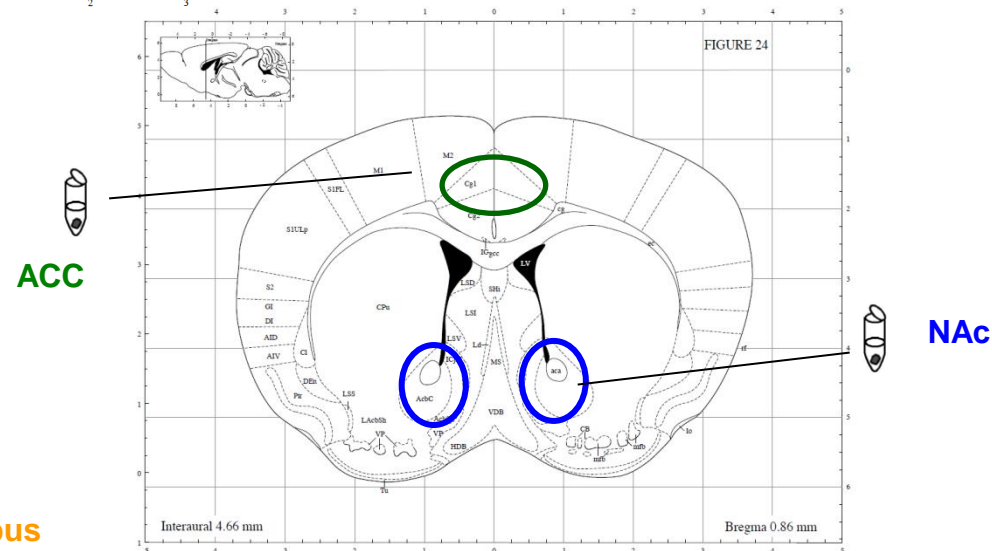
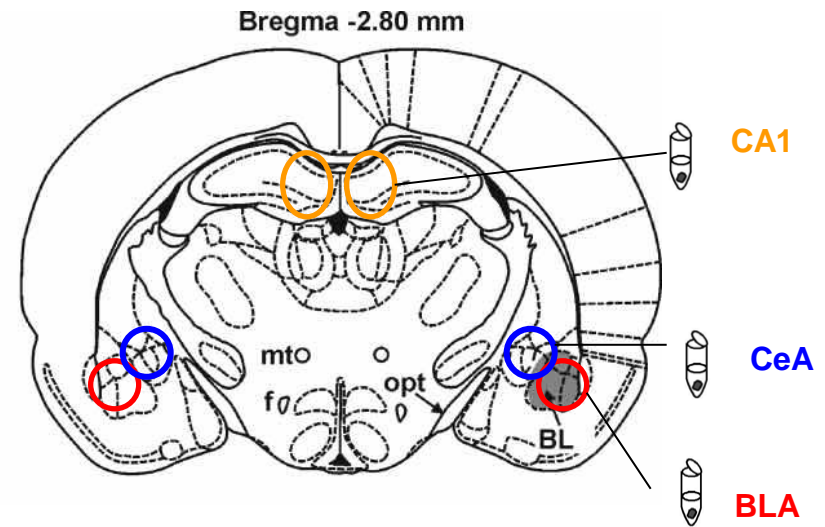
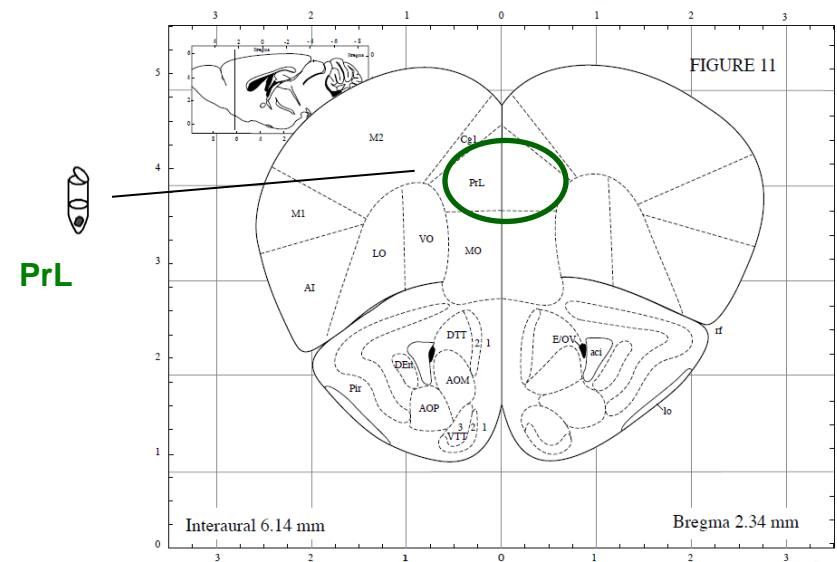
# Neurocircuitry of Fear Regulation

## Brain Punch -Omics

Transcriptome

Proteome

Metabolome



**PrL:** prelimbic cortex  
**ACC:** anterior cingulate cortex  
**NAc:** nucleus accumbens  
**BLA:** basolateral amygdala  
**CeA:** central nucleus of amygdala  
**CA1:** cornu ammonis 1 of hippocampus

**Chi-Ya Kao**  
**Carsten Wotjak**  
**Judith Reichel**  
**Kathrin Henes**

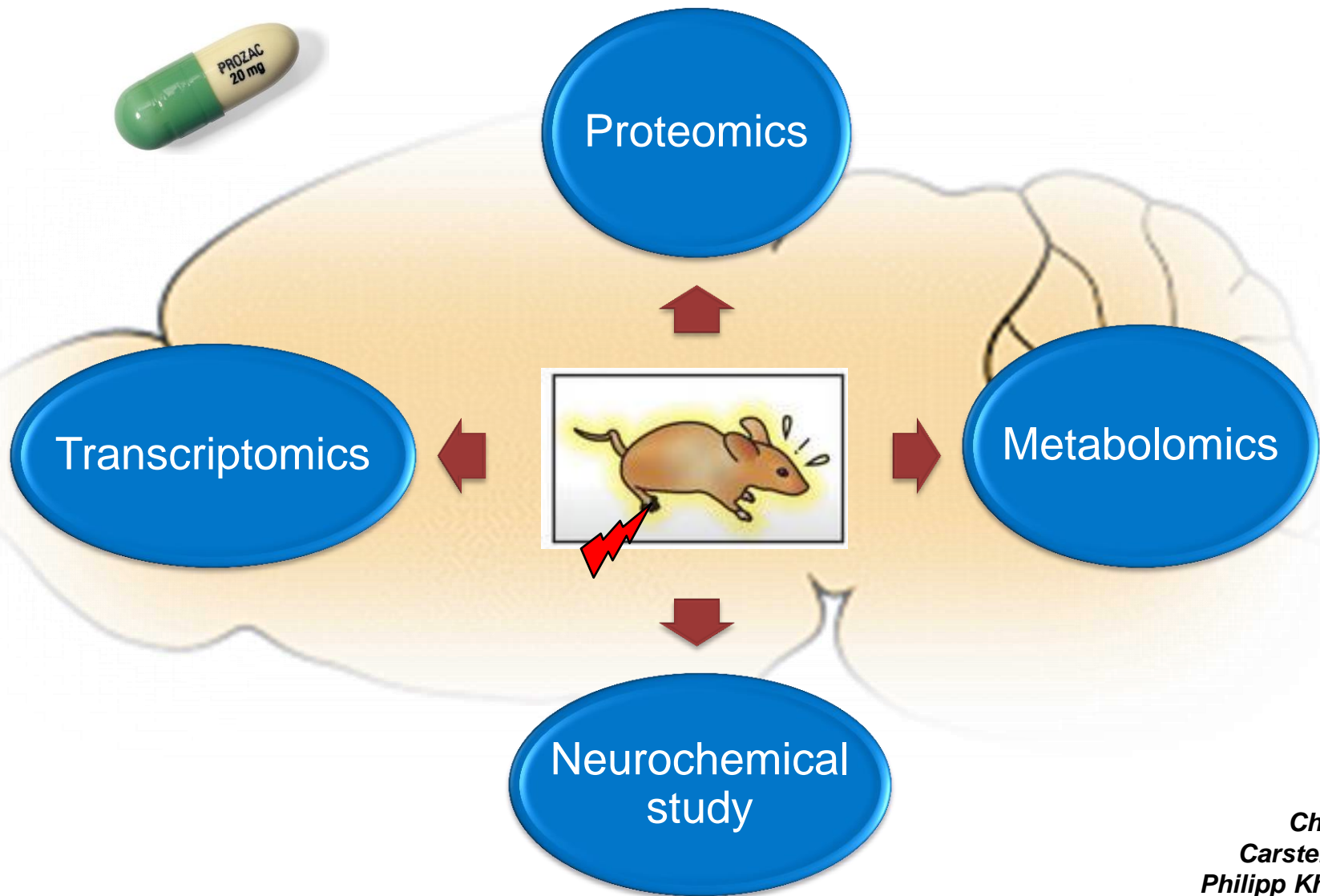
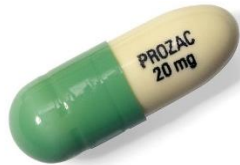
# Neurocircuitry of Fear Regulation

## Brain Punch -Omics

Transcriptome

Proteome

Metabolome

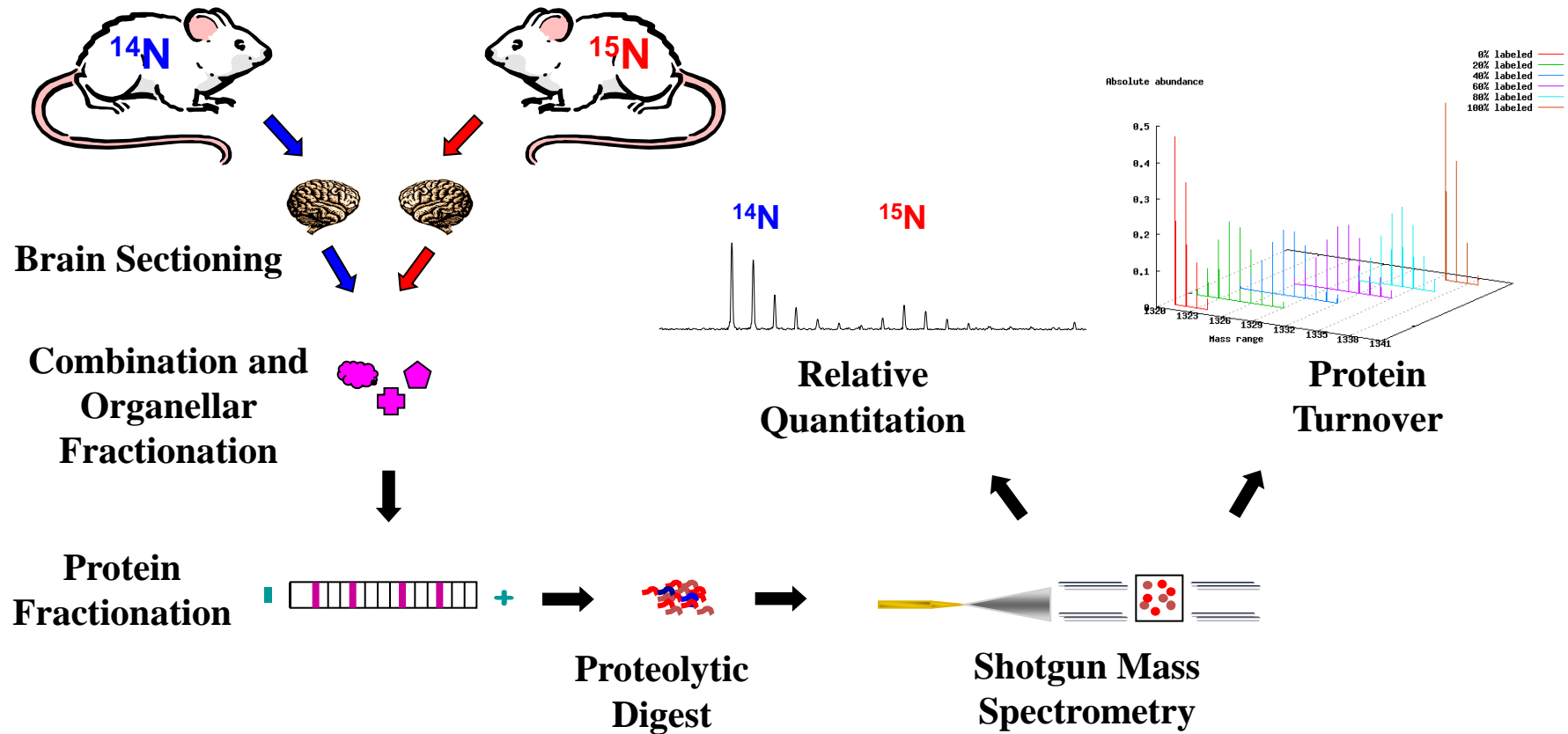


Chi-Ya Kao  
Carsten Wotjak  
Philipp Khaitovich



# Biosignatures

## In-Depth Quantitative Proteomics

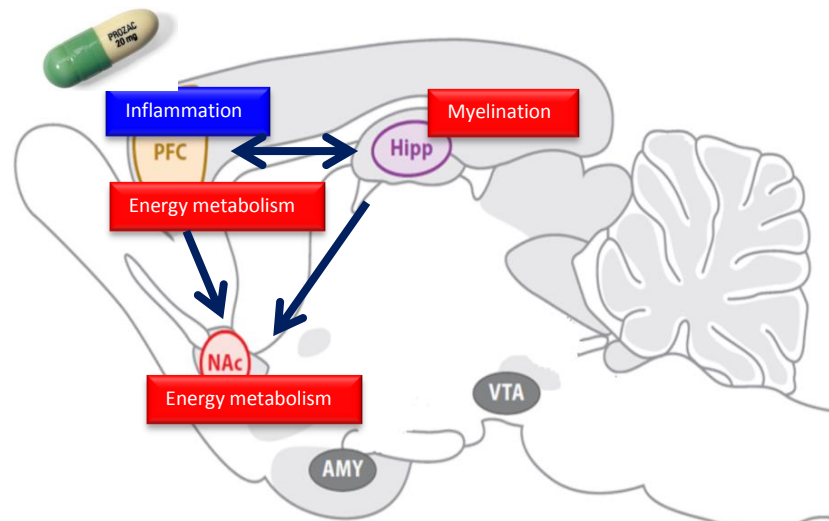




# PTSD Mouse Model



- One month after shock treatment altered pathways related to
  - inflammation, synapse, neurotransmitter release
  - energy metabolism, microtubule cytoskeleton, myelination
- Chronic antidepressant drug treatment ameliorates sensitized fear and pathway dysregulation.
- Extracellular fluid metabolome reflects prefrontal molecular alterations.

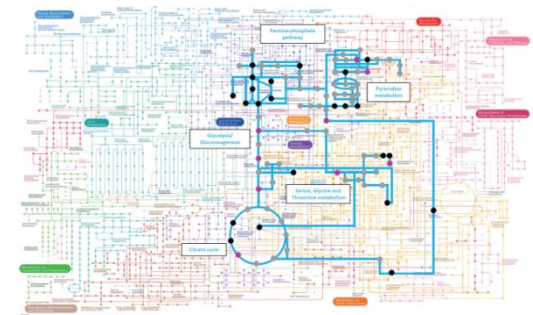
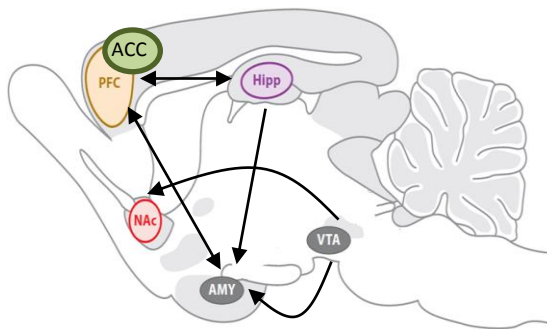
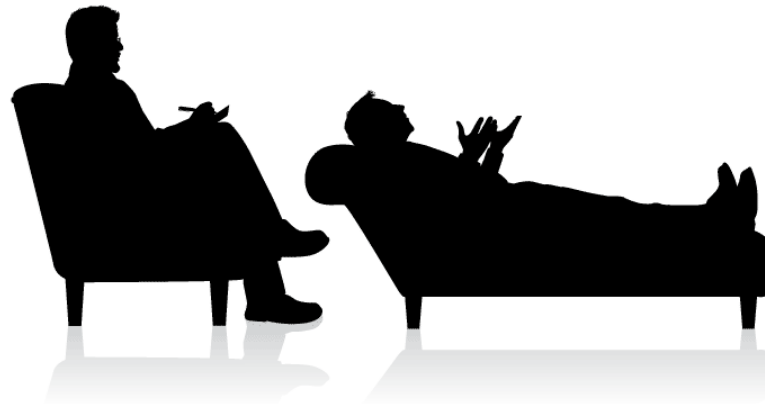


Chi-Ya Kao  
Zhisong He  
Oliver Hahn  
Philipp Khaitovich  
Carsten Wotjak  
Judith Reichel  
Kathrin Henes  
Anthony Zannas  
Elmira Anderzhanova  
John Asara



# “The Unpredictable” Antidepressant Treatment Response

- delineation of molecular pathway activities



# Antidepressant Treatment Response

## - drugs as probes for phenotype

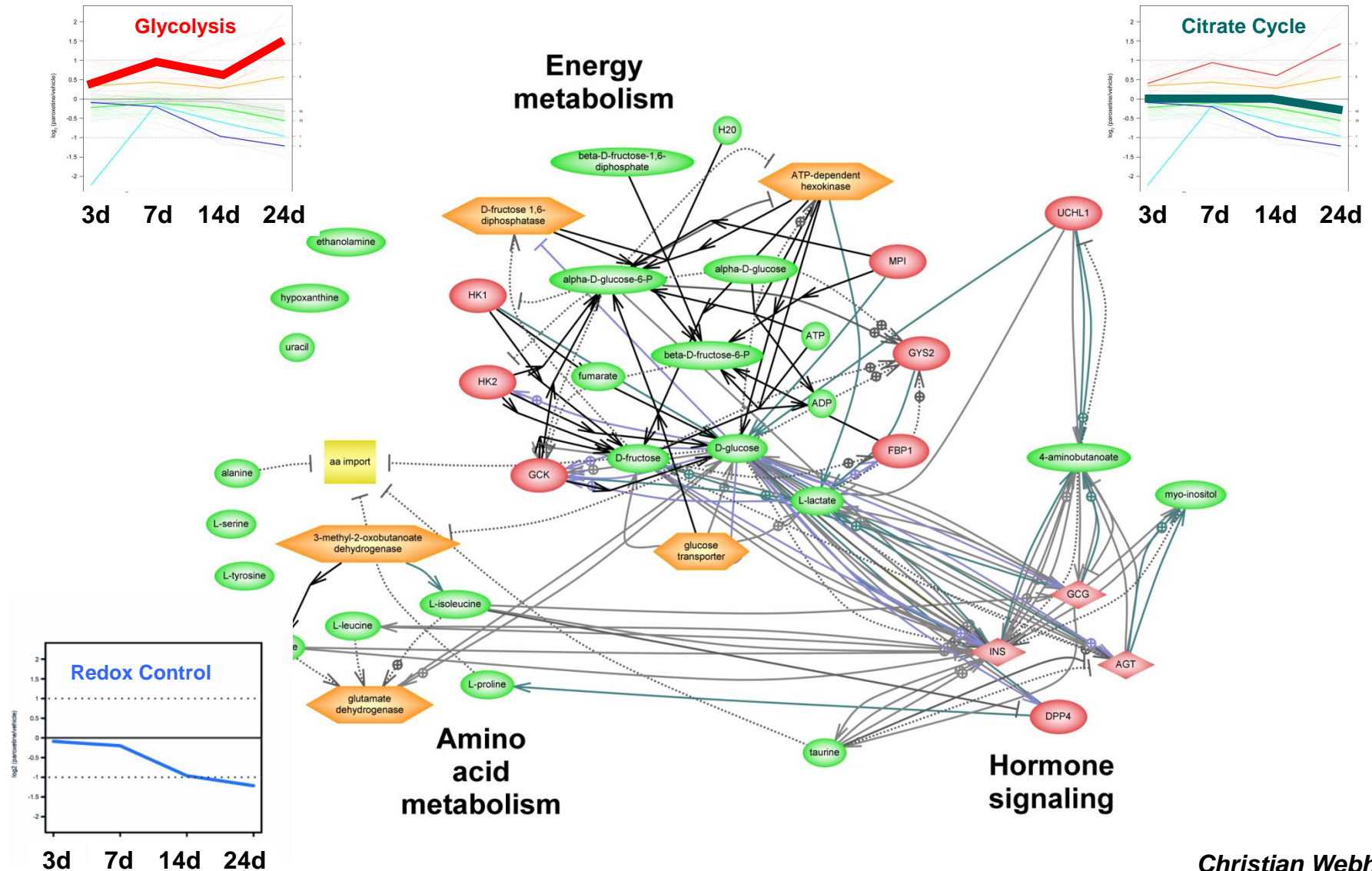


- Majority of patients suffering from Major Depression receive Selective Serotonin Reuptake Inhibitor (SSRI) as first-line treatment.
- SSRI efficacy varies to a large extent, 40% of patients do not respond (defined as 50% reduction of symptoms), 60% do not show complete remission of symptoms.
- Delayed onset and side effects.
- SSRI mechanism of action incompletely understood, especially downstream effects (off pathway effects).
- Biomarkers to predict treatment response are needed for clinical trials and to identify affected downstream pathways.



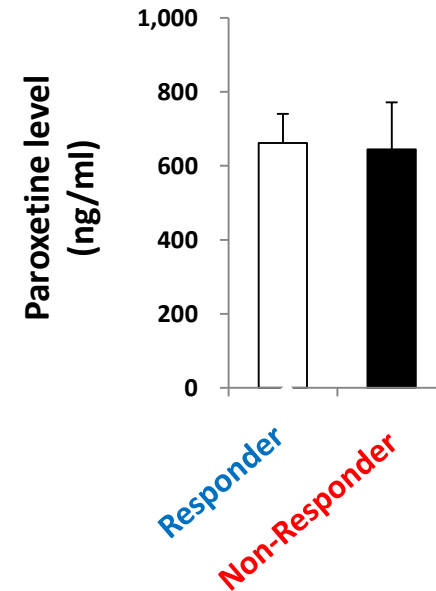
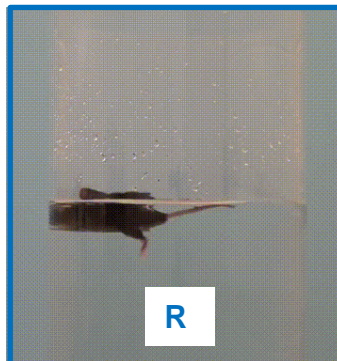
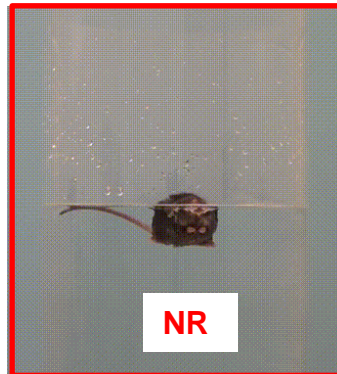
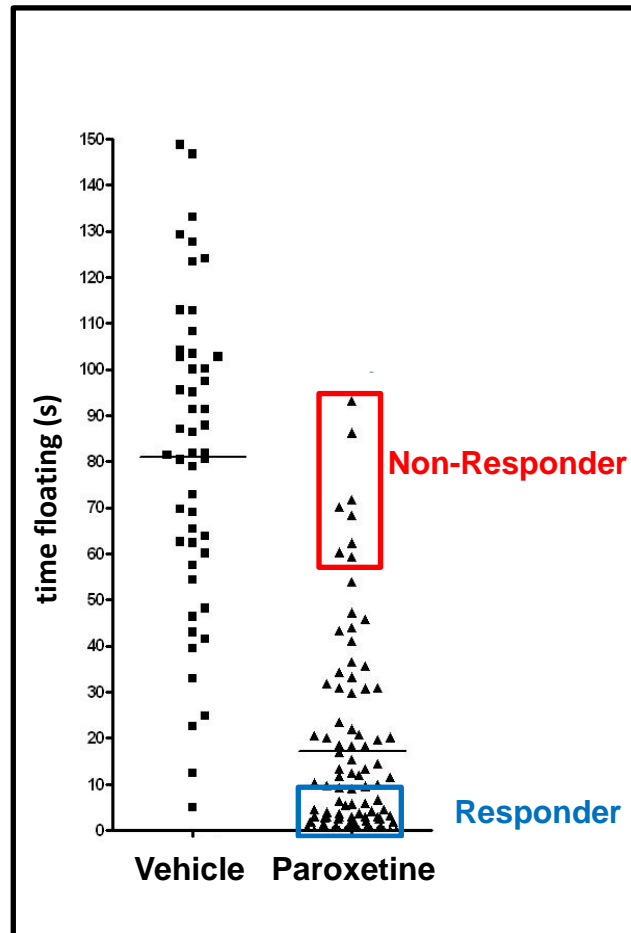
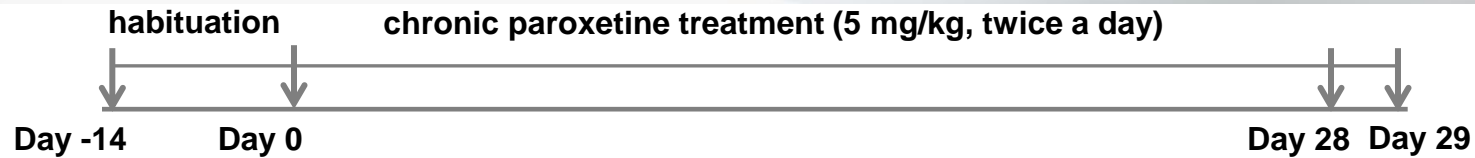
# SSRI Treatment Response

## Metabolome Time Course - Pathways





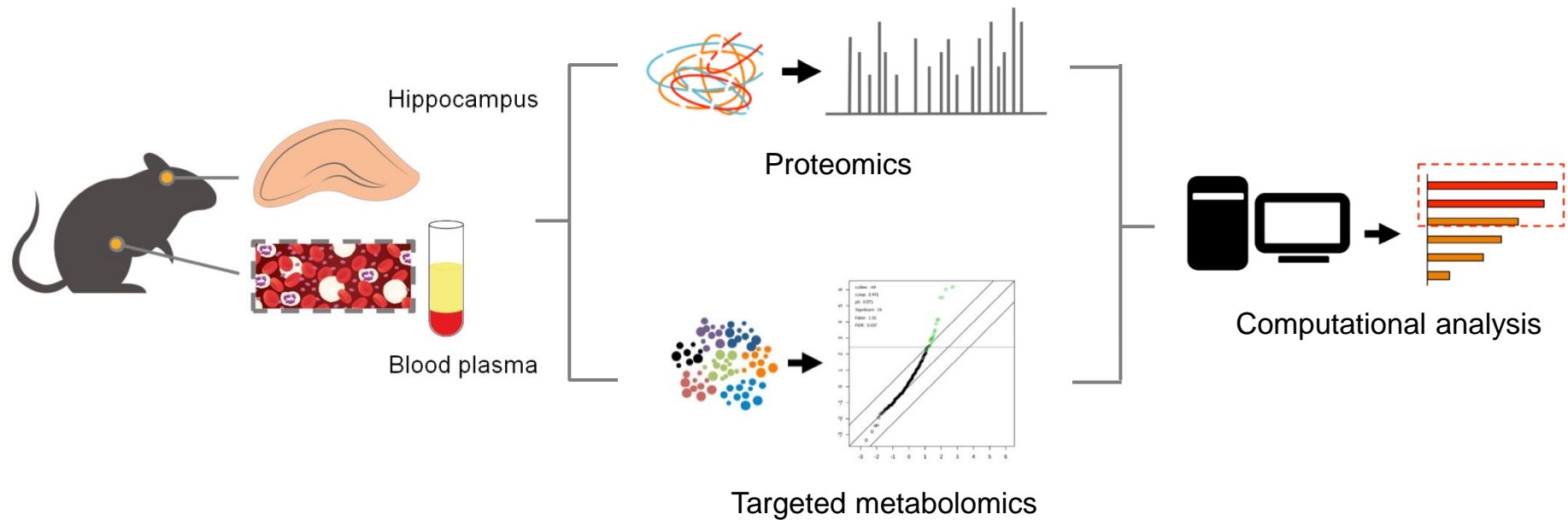
# Responder/Non-Responder Inbred (!) Mice



*Dongik Park  
Marianne Müller  
Christiana Labermaier  
Carine Dournes*



# Response/Non-Response Stratifying Pathways



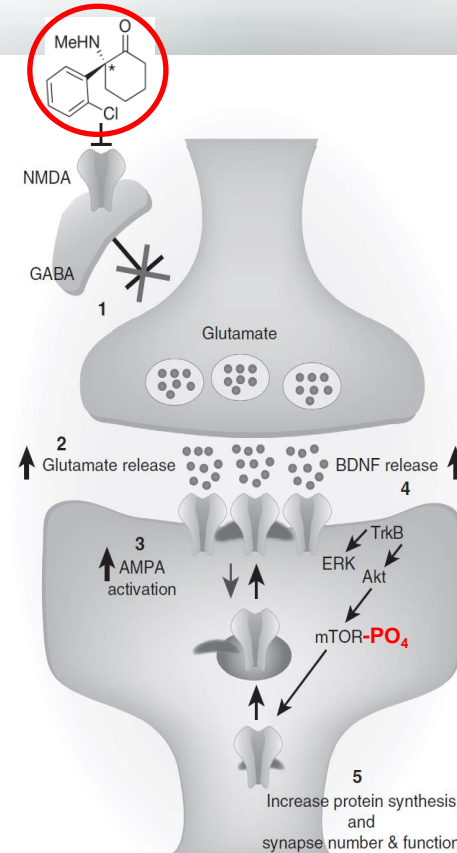
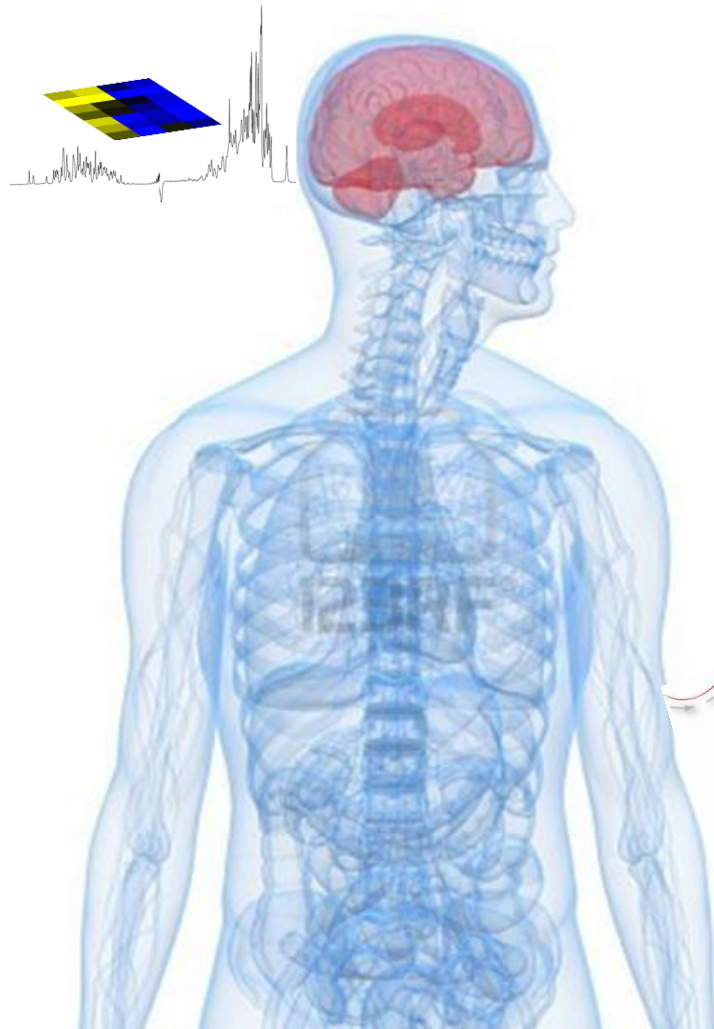
**Dongik Park**  
**Marianne Müller**  
**Christiana Labermaier**  
**Carine Dournes**



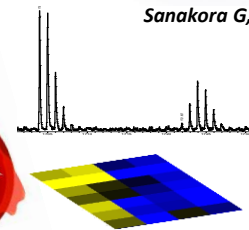
- **SSRI and Ketamine affected pathways implicate energy metabolism and oxidative stress.**
- **Delineation of SSRI response/non-response affected pathways (Purine/Pyrimidine, Glutamatergic, Ubiquitin).**
- **Several CNS treatment response biomarkers can be detected in the periphery.**
- **Ketamine**
  - several shared biomarkers with SSRI response
  - has opposite effect on glycolysis than SSRI (**reason for fast action?**)
  - Hydroxynorketamine metabolite with no side effects

# Towards clinical translation

## Ketamine treatment response case study

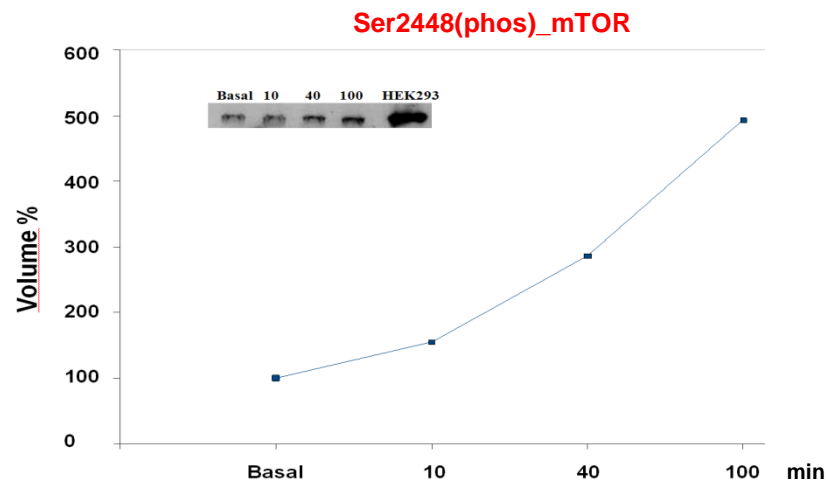
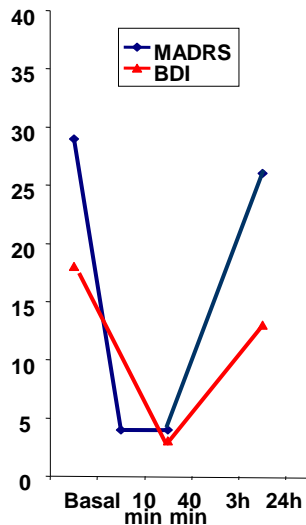
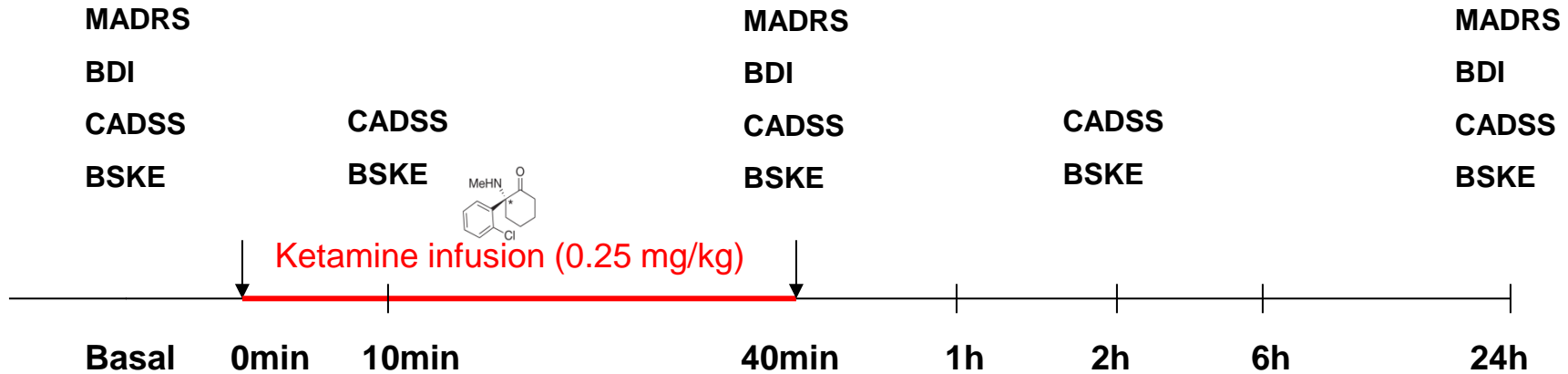


Sanakora G, Schatzberg A (2014) Neuropsychopharmacol 1-9.





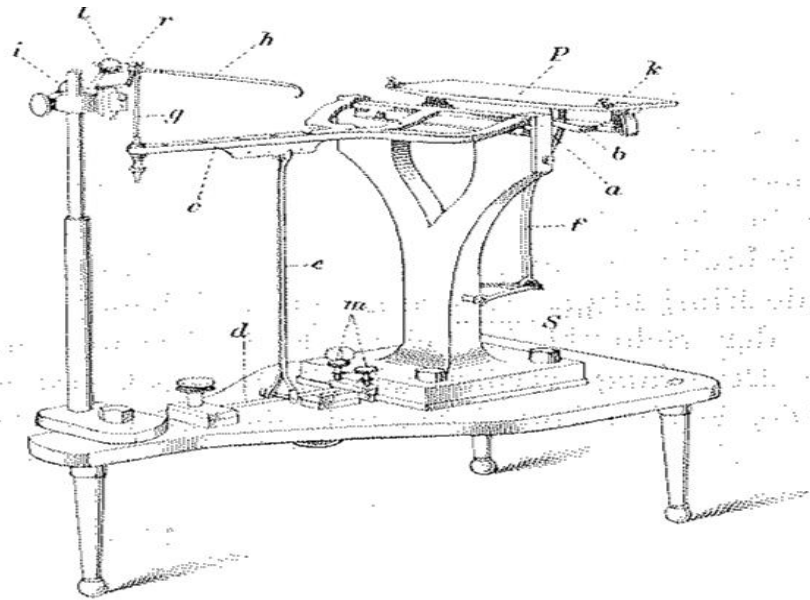
# Ketamine response peripheral monitoring



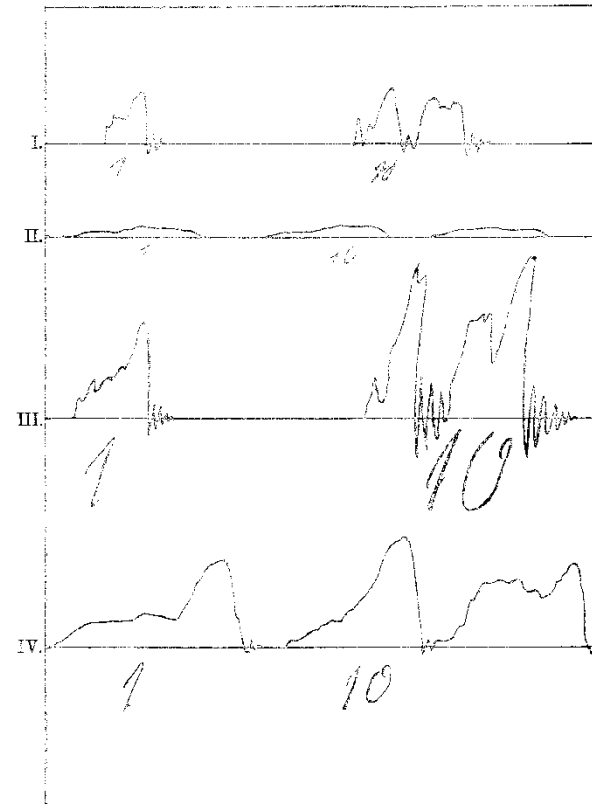
Angelika Erhardt  
Magdalena Denk



## Writing Balance



## Writing Pressure Curves







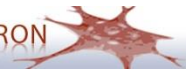
# From Bench to Bedside and Back ...



Federal Ministry  
of Education  
and Research



ERA-NET NEURON



The NIH Common Fund

NGFN

Nationales  
Genomforschungsnetz

Frederik Dethloff  
Claudia Ditzen-Janotta  
Chi-Ya Kao  
Daniel Martins-de-Souza  
Giuseppina Maccarrone  
Dongik Park  
Christiane Rewerts  
Christian Webhofer  
Katja Weckmann



Marianne Müller  
Inge Sillaber  
Carsten Wotjak



Angelika Erhardt  
Marcus Ising  
Manfred Uhr



Zhisong He  
Oliver Hahn  
Philipp Khaitovich