

Ingo Vernaleken

**Nicotine Abuse in
Schizophrenia - Molecular Aspects**



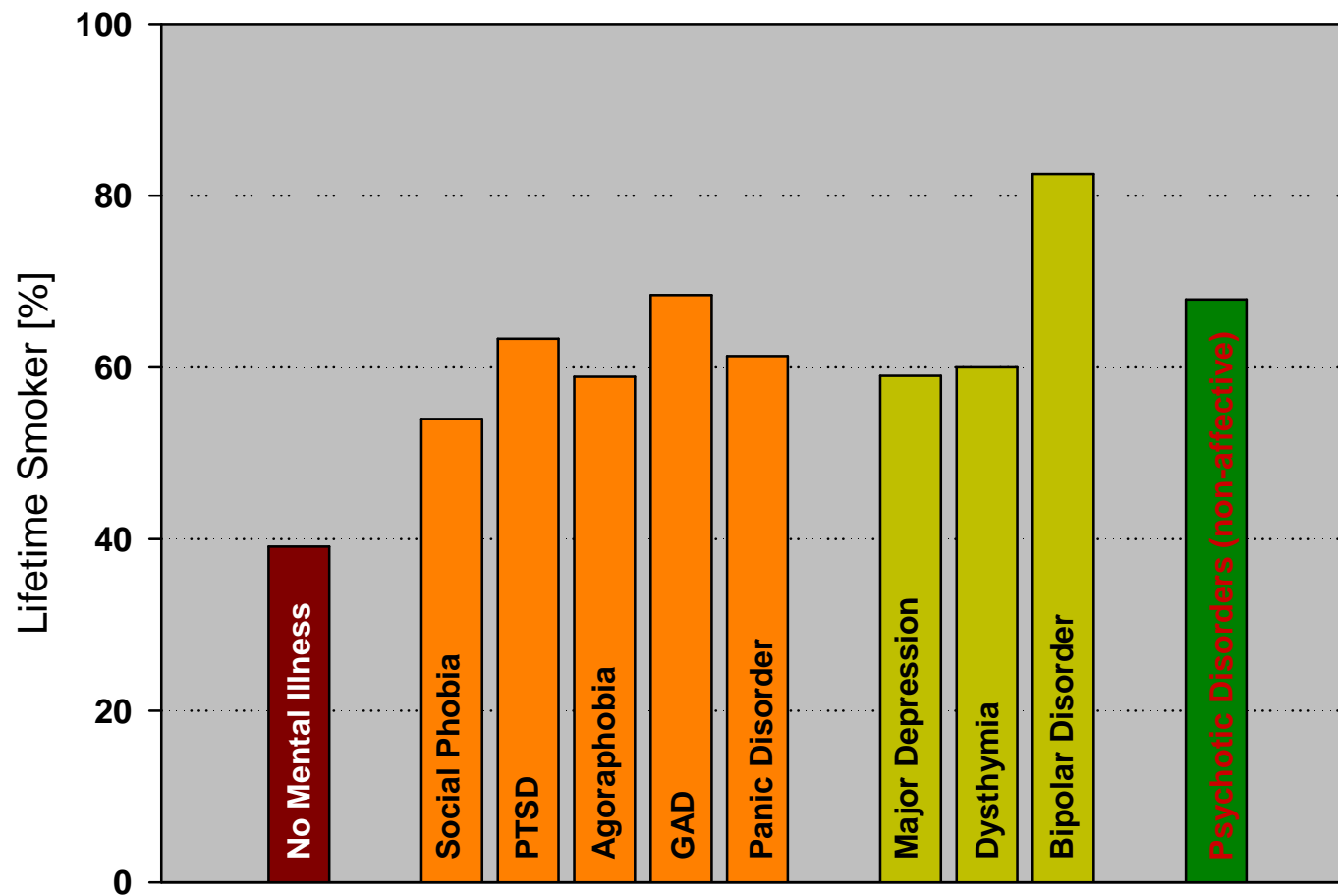
Edinburgh, 26th April, 2009

Smoking Prevalence in Psychiatric Disorders

- **Patients suffering from schizophrenia show higher comorbidity to substance dependence or abuse**
- **Beside caffeine, nicotine is the most common substance of abuse**
- **Usually cigarette smoking begins 5 years before first diagnosis of schizophrenia**
- **Smoking patients show worse outcome in treatment**

Smoking Prevalence in Psychiatric Disorders

Representative Analysis of 4411 subjects (NCS)



According to data of Lasser et al. 2000

Smoking Prevalence in Psychiatric Disorders

Possible Reasons for high Comorbidity Rates:

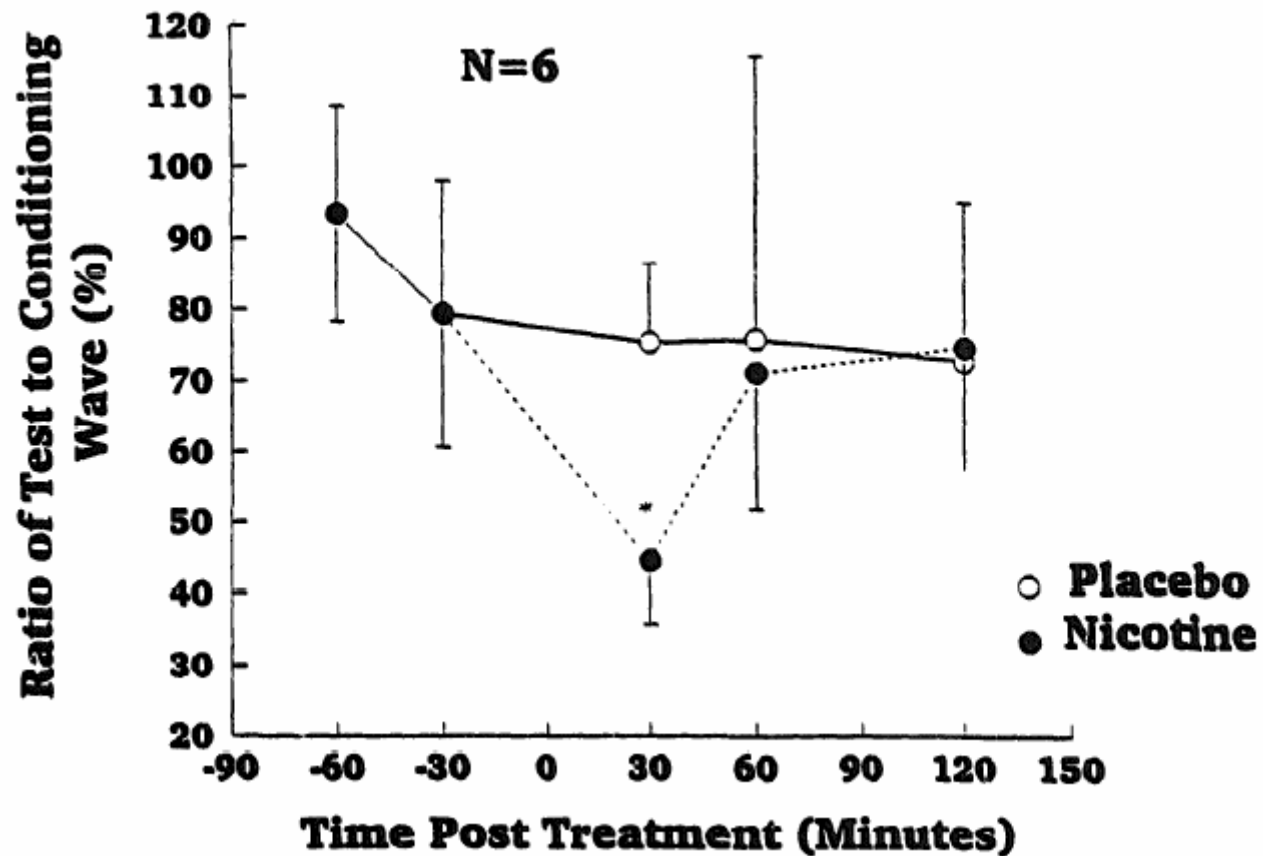
- **Self Medication of Cognitive Deficits and/or Negative Symptoms**

- **Psychosocial factors**
 - **low or bad peer influence**
 - **increased idle time**
 - **less familiar support**
 - **lower psychosocial status**

- **Related or common etiopathological factor of schizophrenia and (nicotine-addiction)**

Nicotinic Modulation of P50 Auditory Evoked Response

Relatives of Patients with Schizophrenia
(6 mg nicotine per os)



Nicotinic Modulation of Cognition in Healthy Subjects

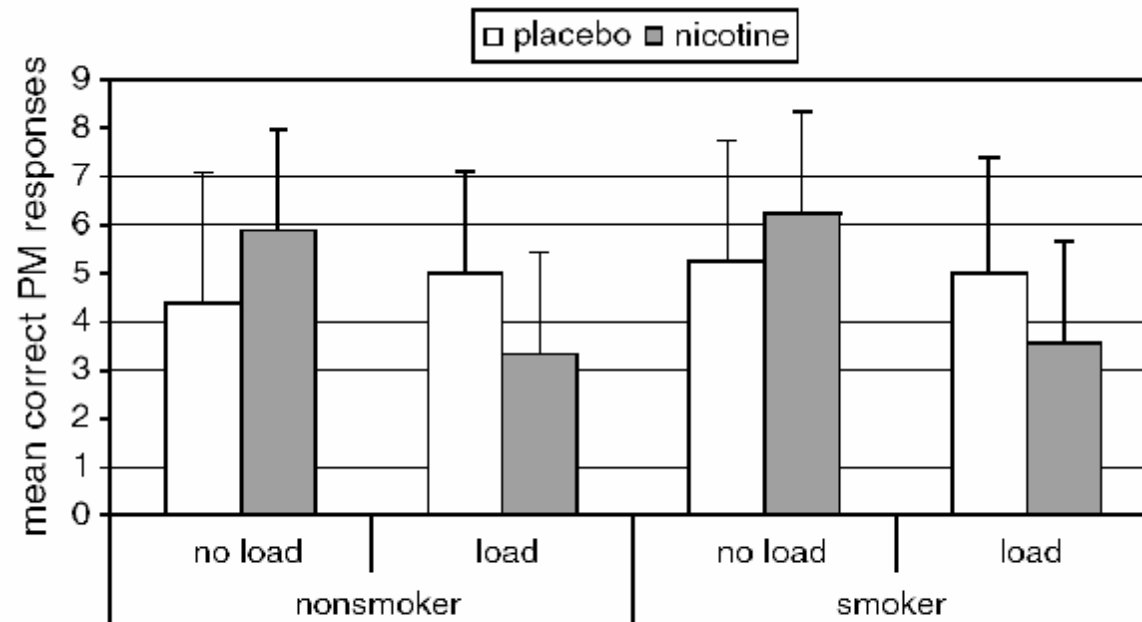
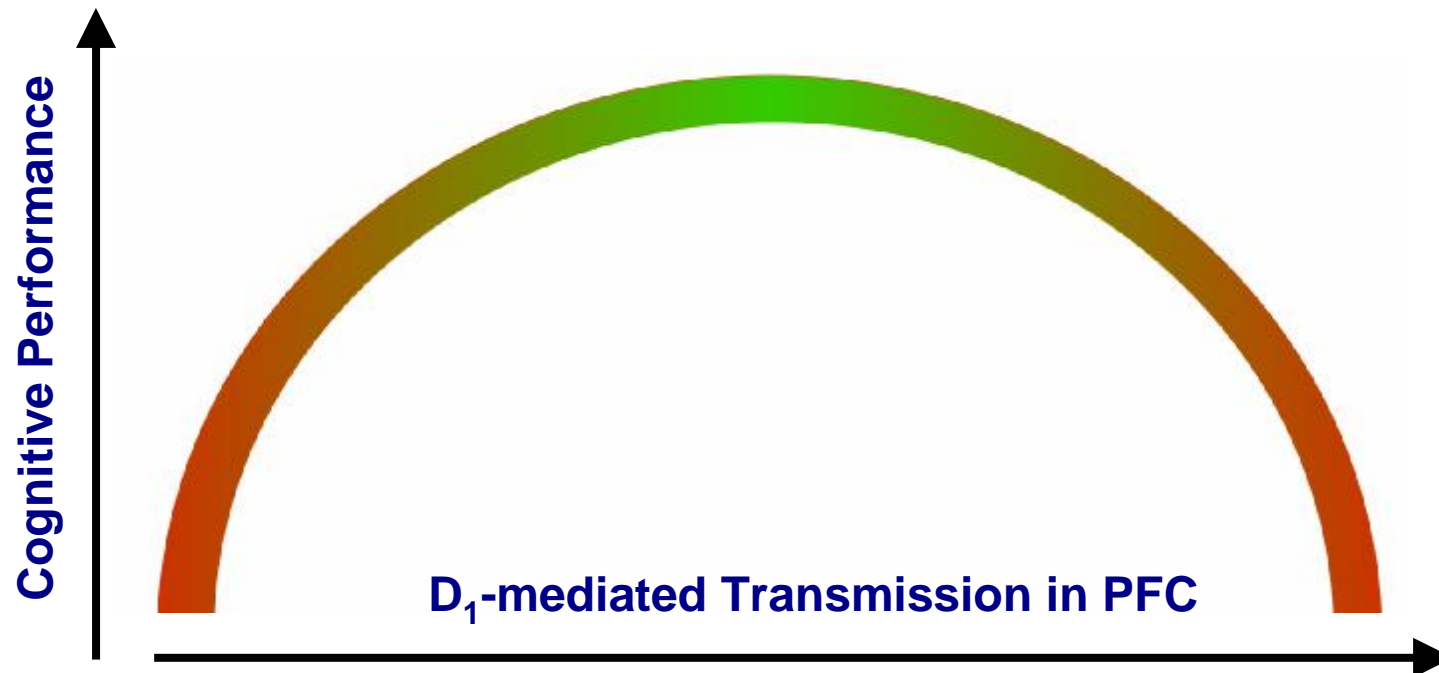


Figure 1 Mean ProM targets correctly identified as a function of group nicotine condition, and WM load.

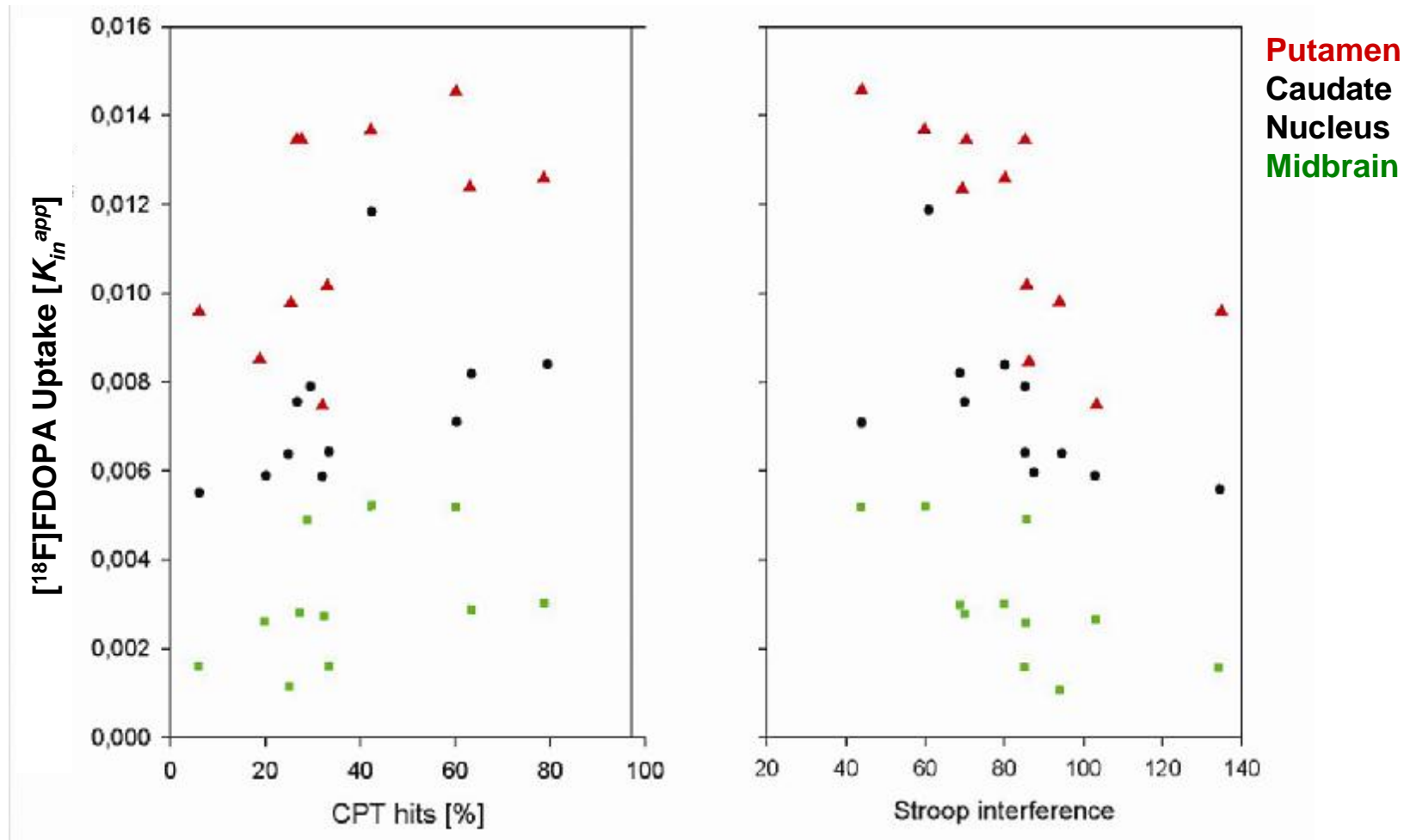
Dopamine and Cognition

- Inverse u-shape relationship between cognition and D_1 -receptor mediated transmission
- Also D_2 -receptor mediated transmission shows state-dependent effects



Dopamine Synthesis Capacity and Cognition

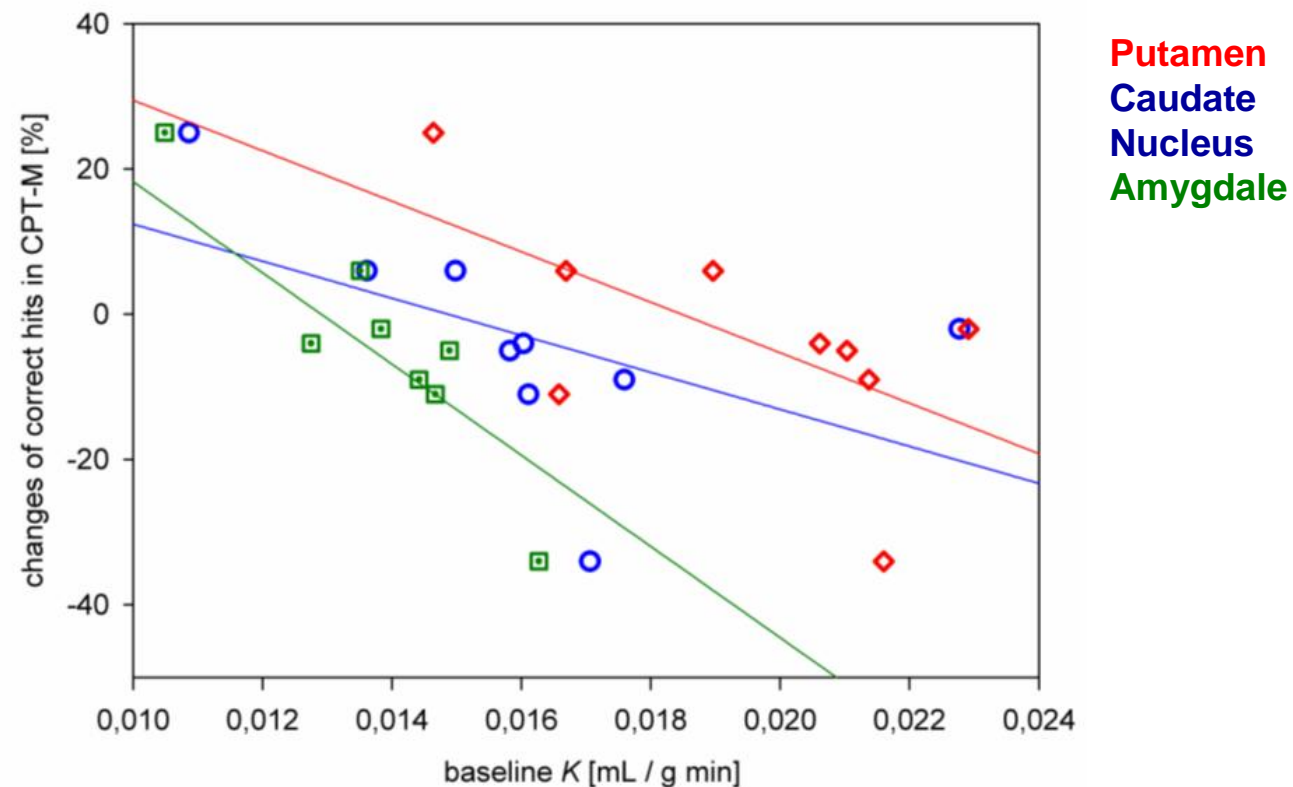
[¹⁸F]FDOPA-Uptake in Healthy Subjects (n=11)



Vernaleken et al. 2007

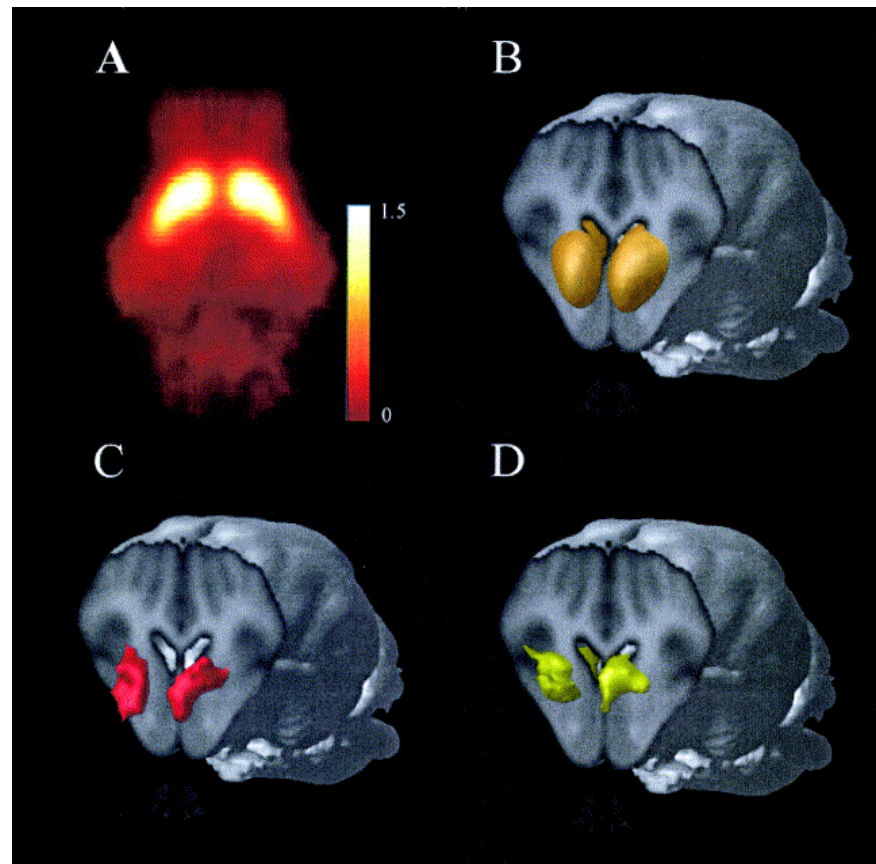
Complex Modulation of Dopamine – Cognition Interaction

Acute Haloperidol Effect (3 days) on Cognition in Healthy Subjects (n=9)



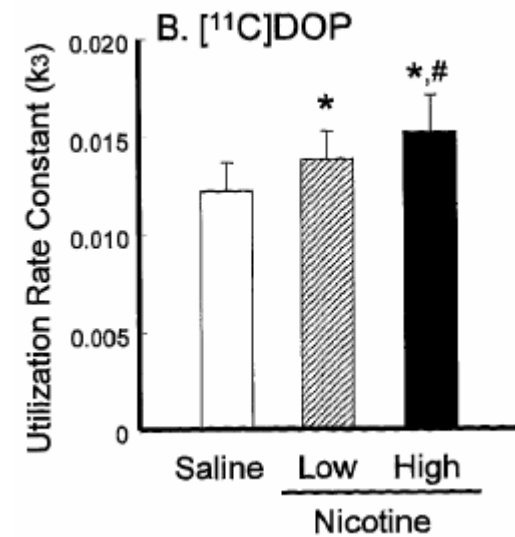
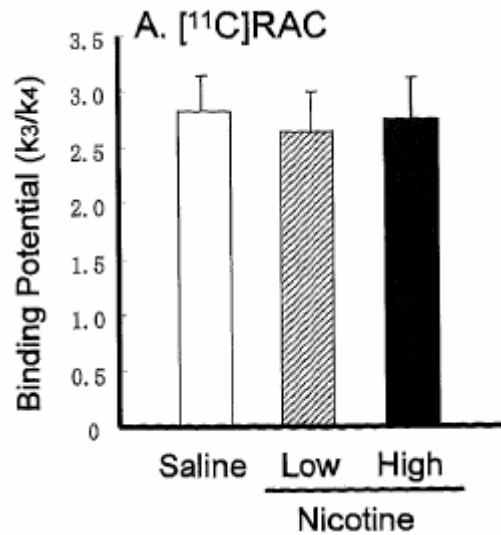
PET-Results in Pigs (Isoflurane Anesthesia)

Effect of Nicotine Injection (500 μ g/kg)
on [11 C]raclopride Binding in the Striatum



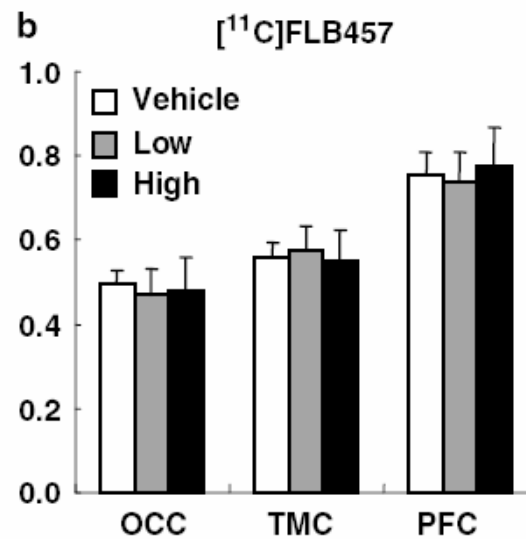
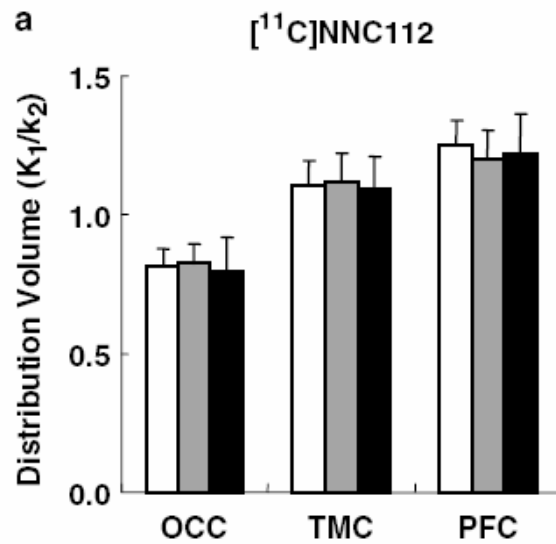
D_{2/3} vs. DOPA-PET

Nicotine Effects in Monkey Brain

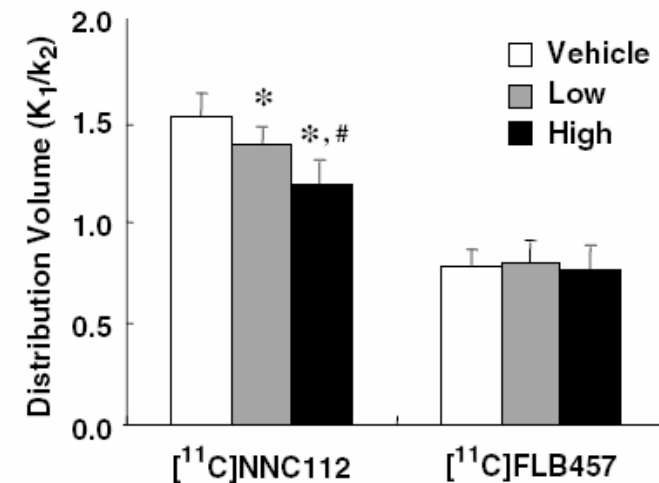


Nicotine Effects after MK-801 Treatment

MK-801 Effect on D₁- and D₂-Receptor Binding

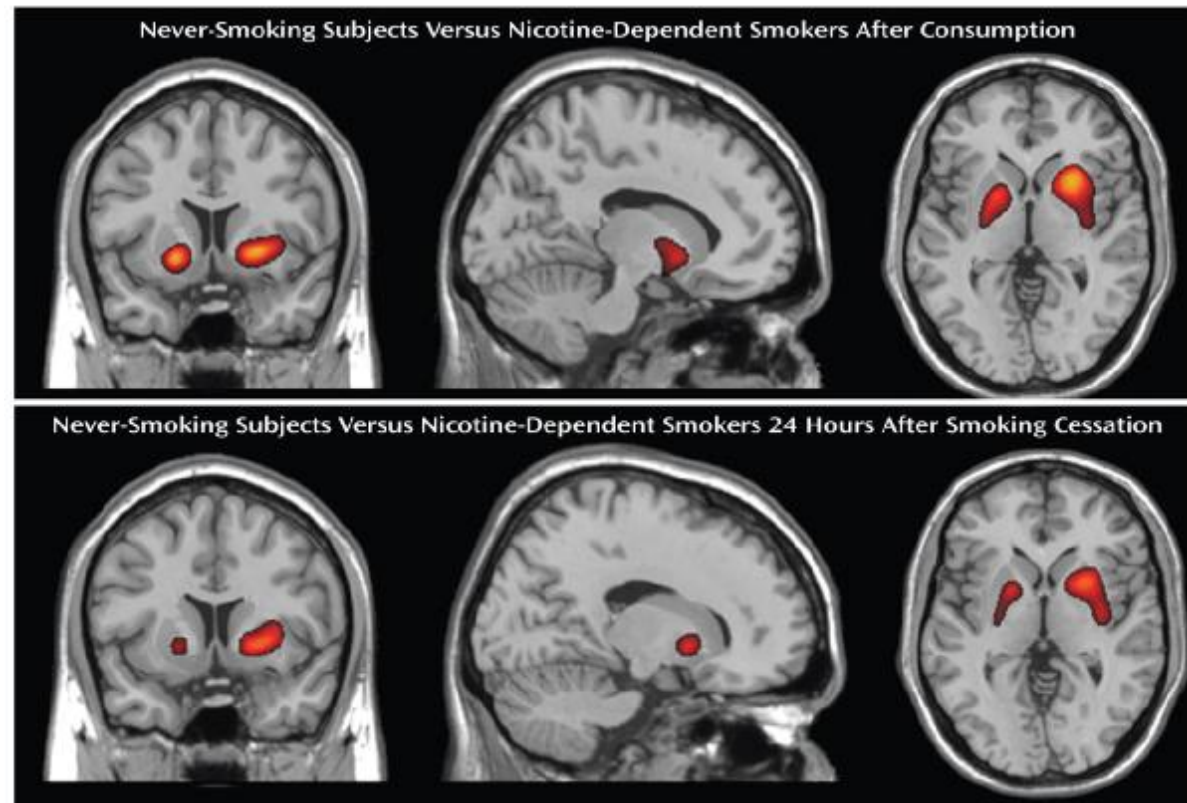


Nicotine Effect after MK-801 Treatment



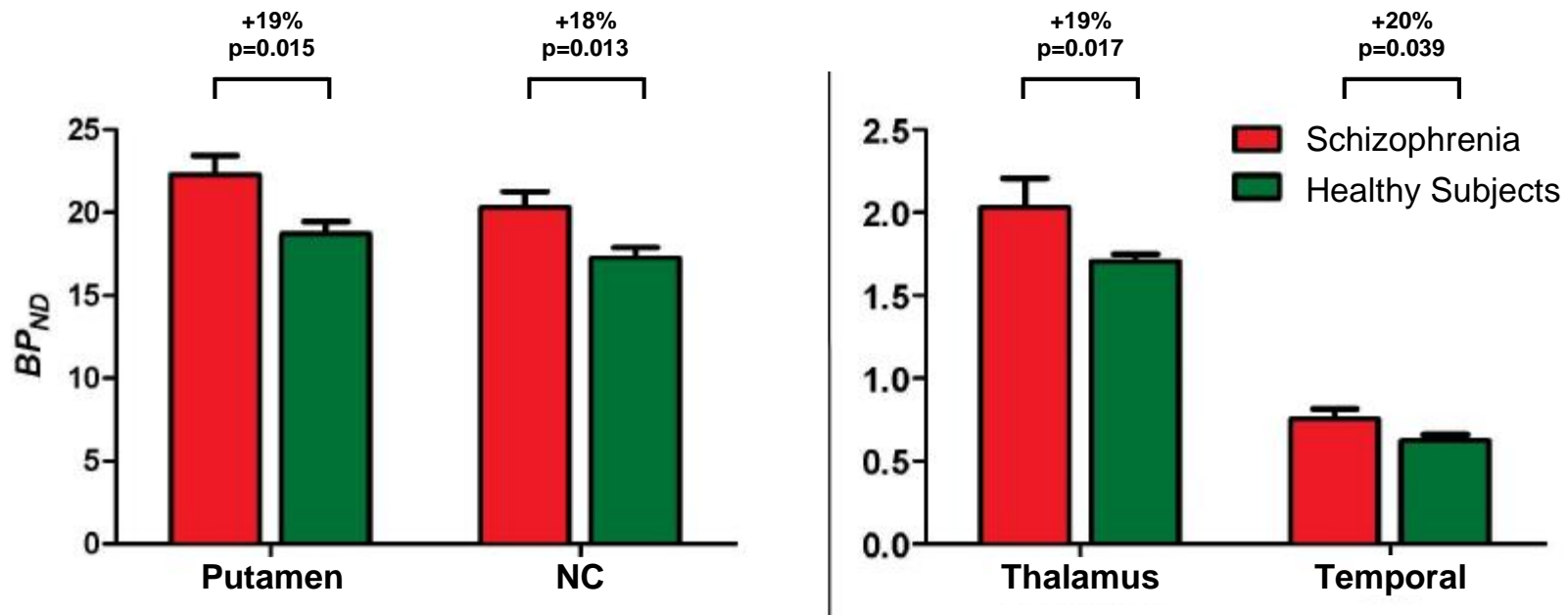
Baseline Dopamine System in Smokers

Differences in Dopamine D_{2/3} Receptor Availability
(Never-Smoking Subjects vs. Smokers After Consumption and Withdrawal)



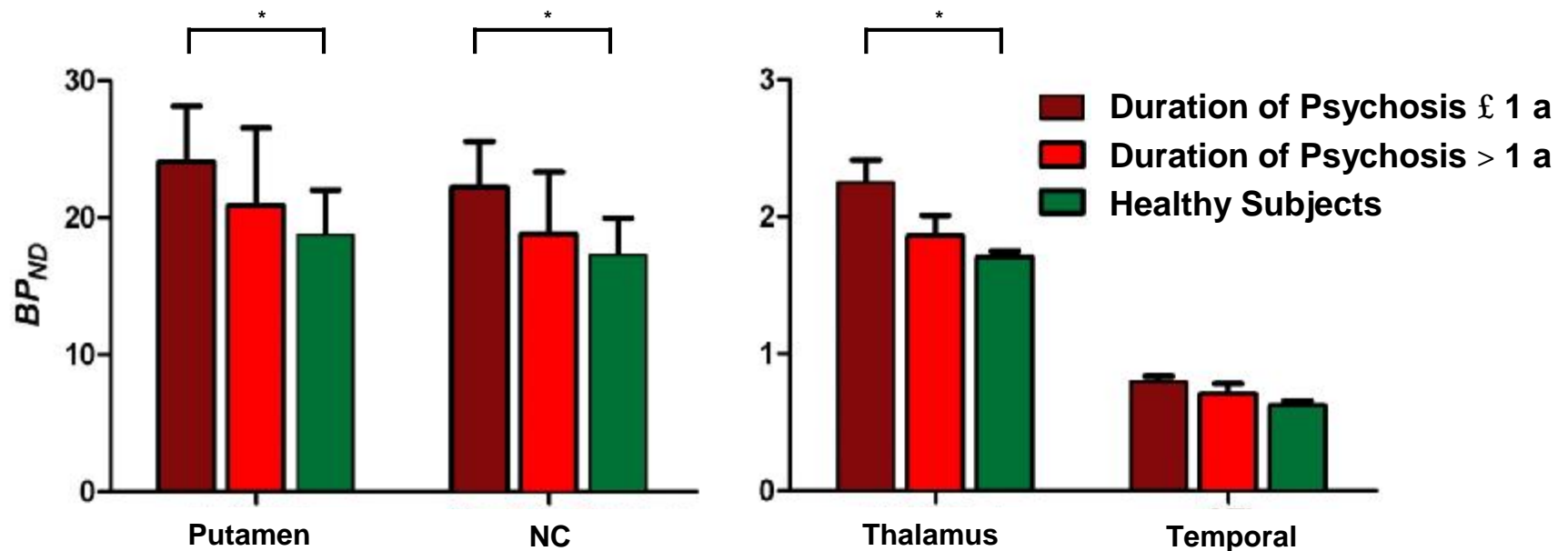
Dopaminergic (Dys)-Regulation in Schizophrenia

D_{2/3}-Receptor-Availability of Drug-free Patients (n=20/18)



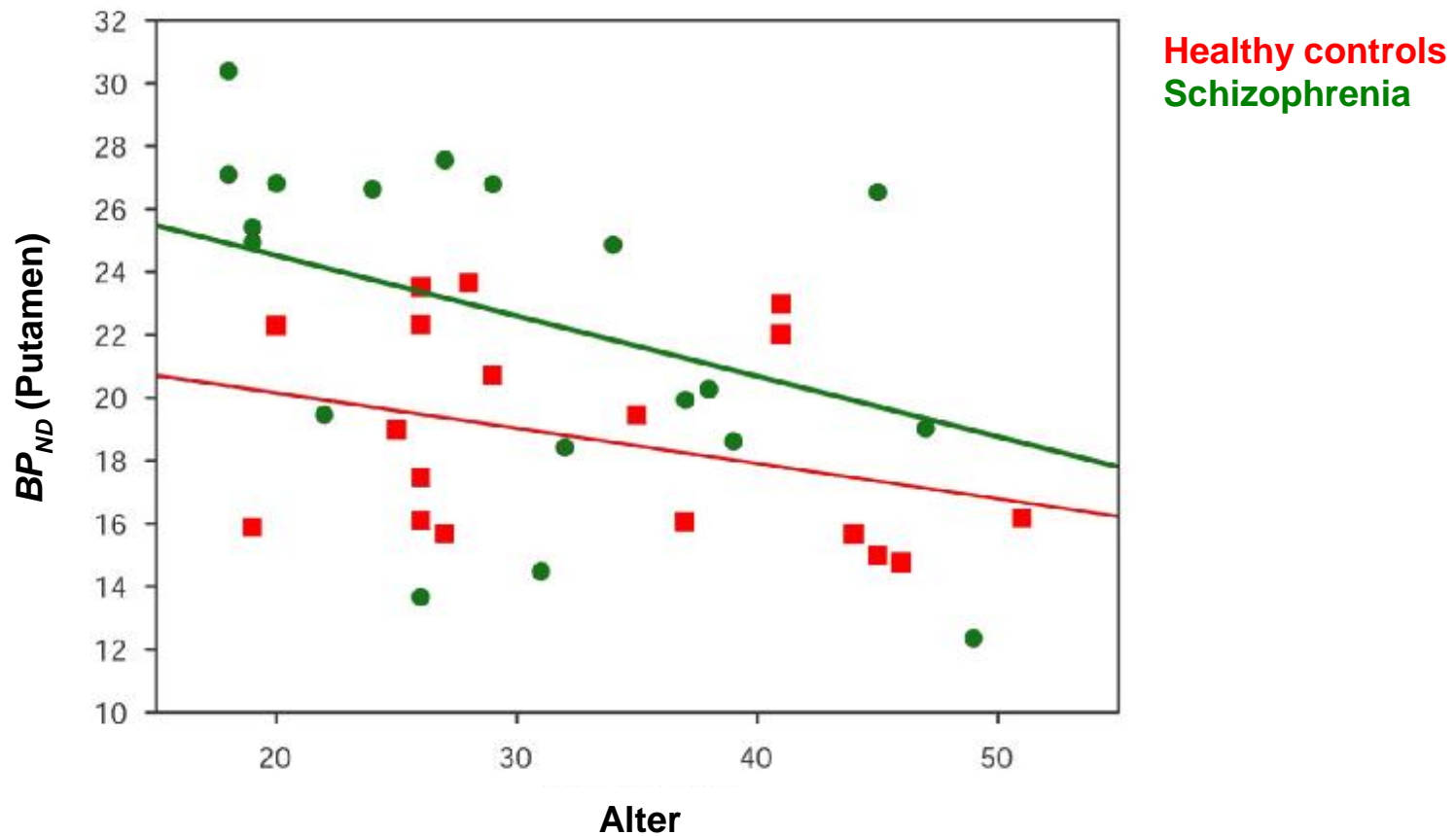
Dopaminergic (Dys)-Regulation in Schizophrenia

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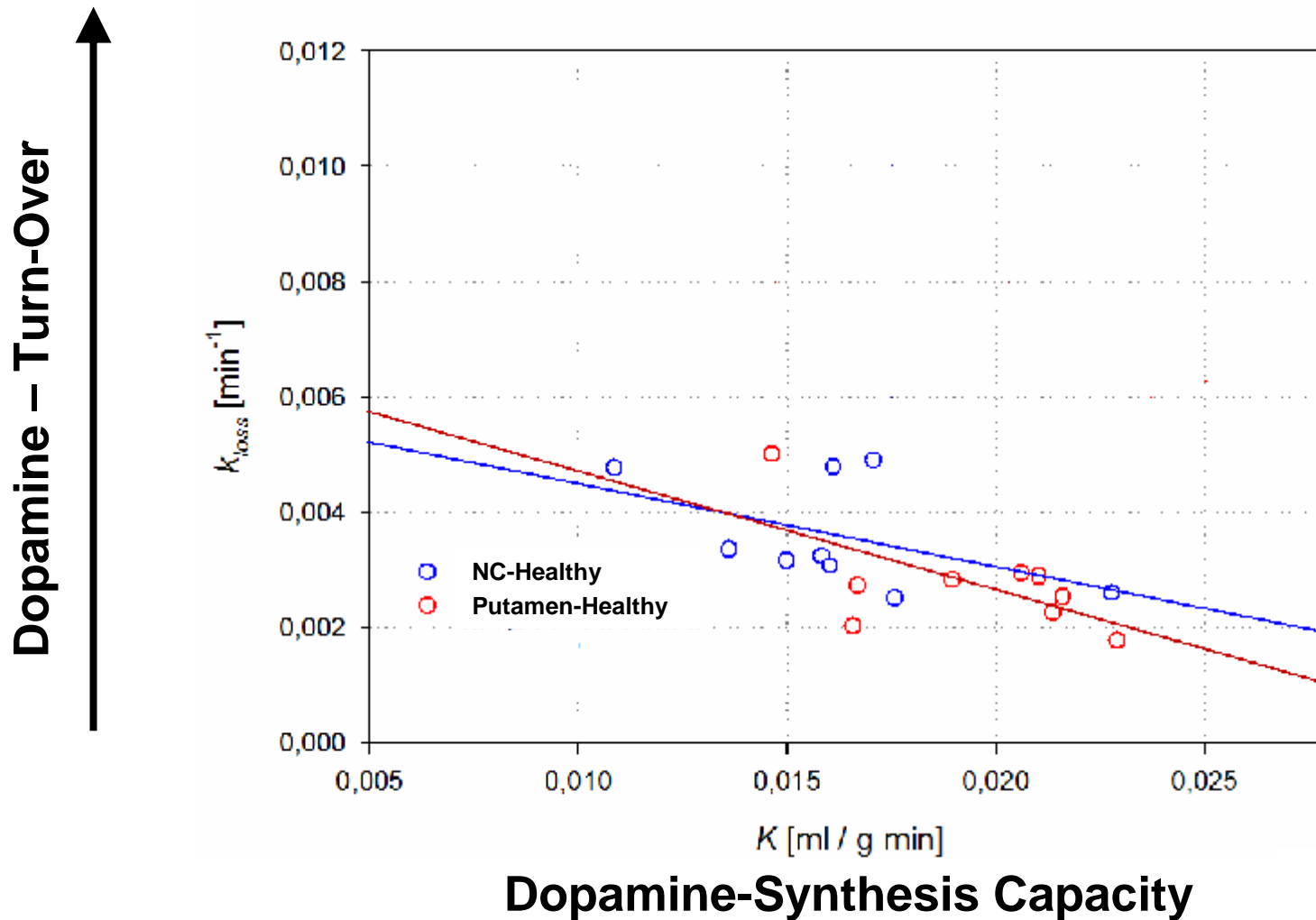
Dopaminergic (Dys)-Regulation in the Course of Schizophrenia

D_{2/3}-Receptor-Availability in Unmedicated Patients (n=20)



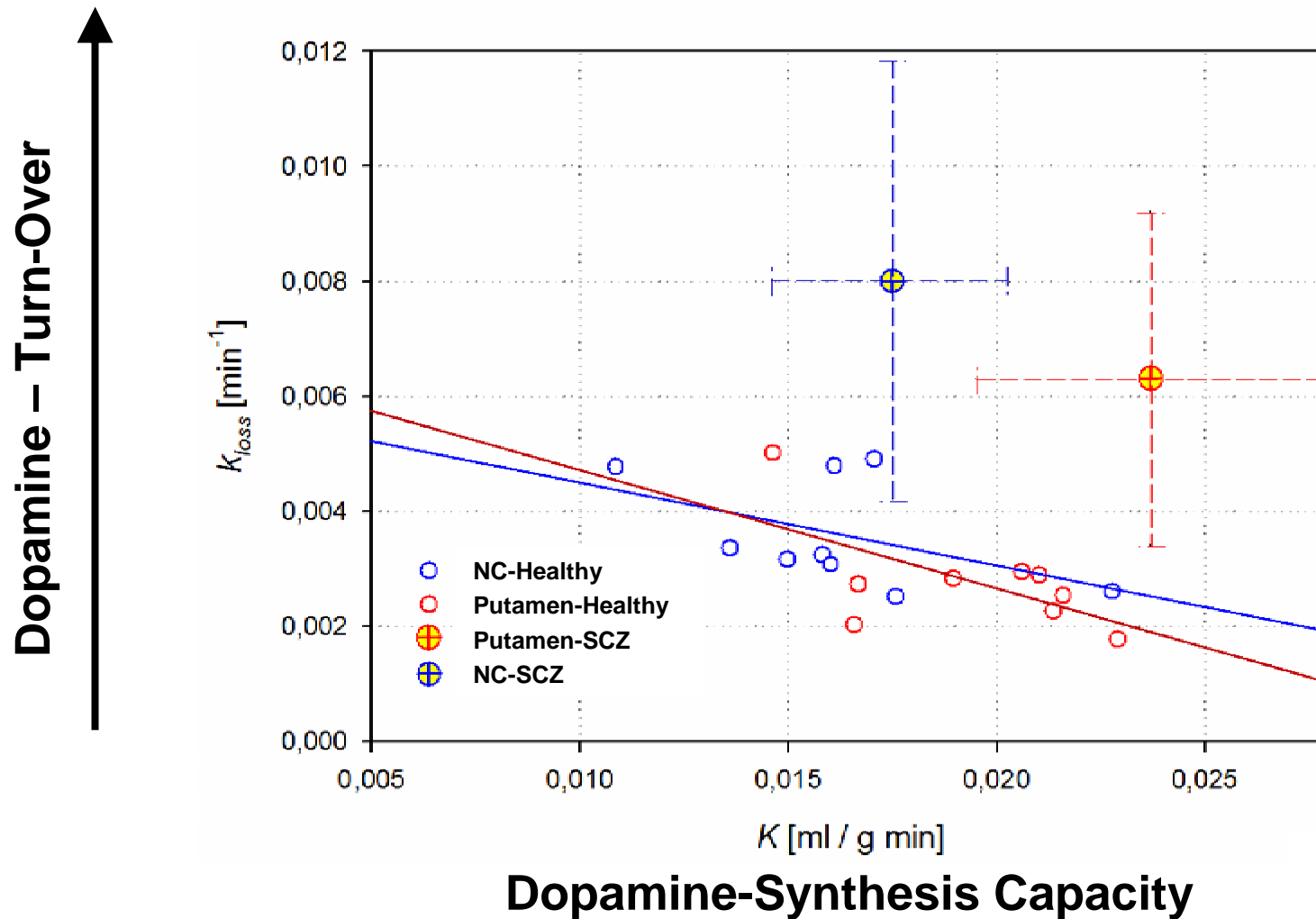
Dopaminergic Homeostasis

Dopamine Synthesis Capacity vs. Turnover



Dopaminergic Homeostasis

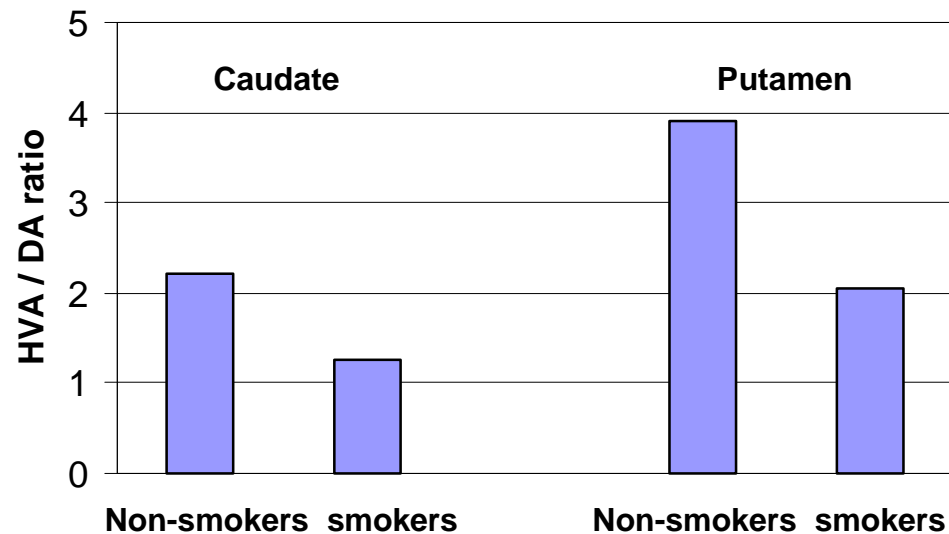
Dopamine Synthesis Capacity vs. Turnover



Baseline Dopamine System in Smokers

Post-Mortem Results of Smokers

HVA / DA Ratio in smokers and non-smokers



No significant differences in dopamine receptor binding

According to data of Court et al. 1998

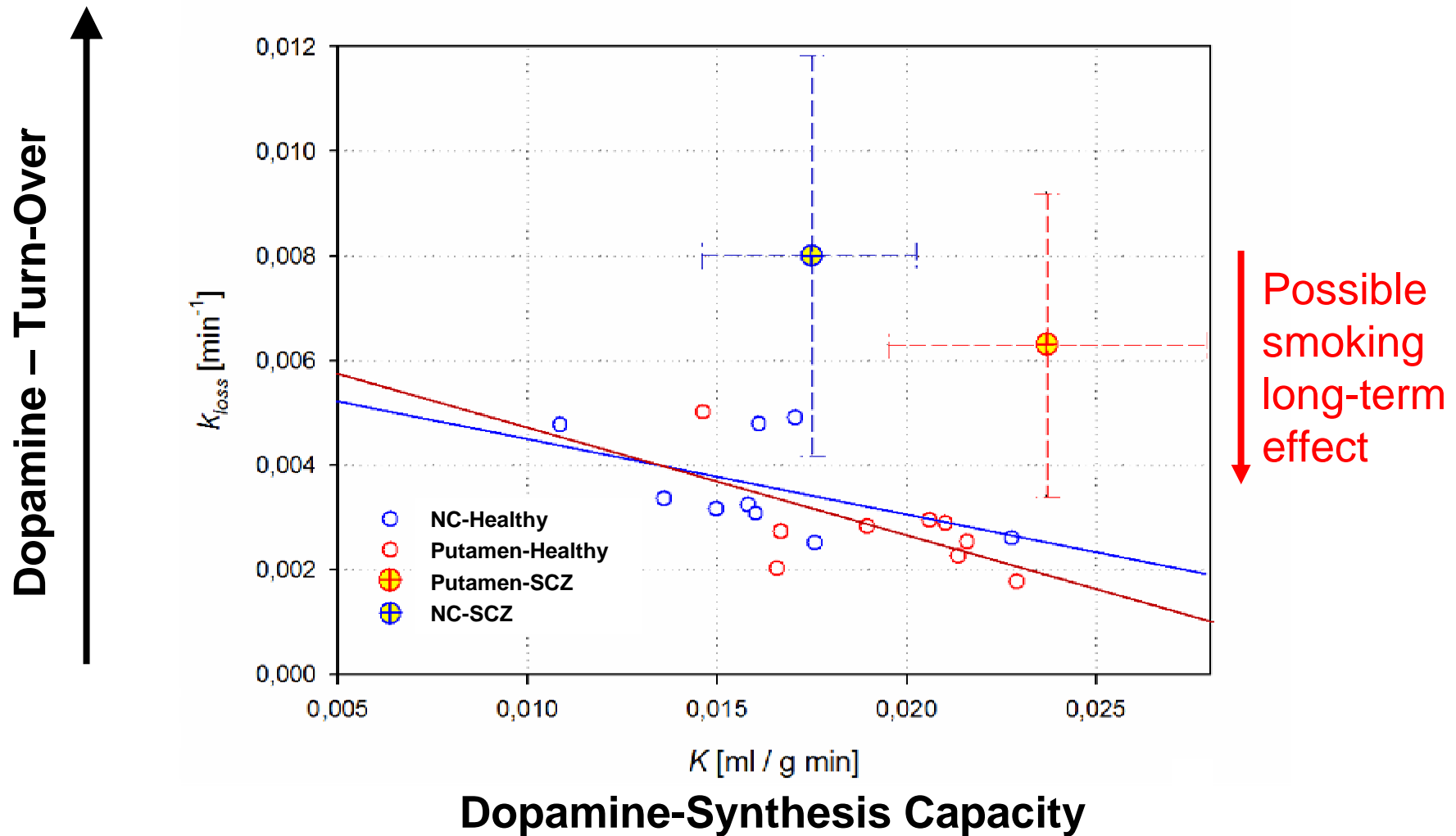
Smoking and MAO-A Availability

[¹¹C]befloxatone availability in 7 healthy smokers vs. 6 nonsmokers

Region	K1		z Value	P	BP (k3/k4)		% Difference	z Value	P
	Nonsmokers (Mean ± SD)	Smokers (Mean ± SD)			Nonsmokers (Mean ± SD)	Smokers (Mean ± SD)			
Cingular cortex	0.28 ± 0.03	0.26 ± 0.04	-0.71	0.5	32.2 ± 13.1	13.8 ± 3.1	-57%	-2.86	0.004
Frontal cortex	0.28 ± 0.02	0.26 ± 0.04	-1.71	0.1	28.4 ± 12.0	11.6 ± 2.6	-59%	-2.86	0.004
Occipital cortex	0.29 ± 0.03	0.28 ± 0.03	-0.14	0.9	30.1 ± 12.1	12.5 ± 2.6	-59%	-3.00	0.003
Cerebellum	0.25 ± 0.03	0.25 ± 0.04	-0.55	0.6	14.9 ± 5.8	6.0 ± 1.5	-60%	-2.74	0.006
Caudate	0.24 ± 0.02	0.25 ± 0.03	-0.14	0.9	10.4 ± 4.4	6.1 ± 2.1	-41%	-1.71	0.09
Putamen	0.27 ± 0.01	0.28 ± 0.03	-1.43	0.2	16.9 ± 6.8	10.6 ± 3.5	-38%	-1.43	0.15
Thalamus	0.28 ± 0.02	0.29 ± 0.03	-0.71	0.5	12.1 ± 5.1	7.4 ± 2.3	-39%	-1.71	0.09

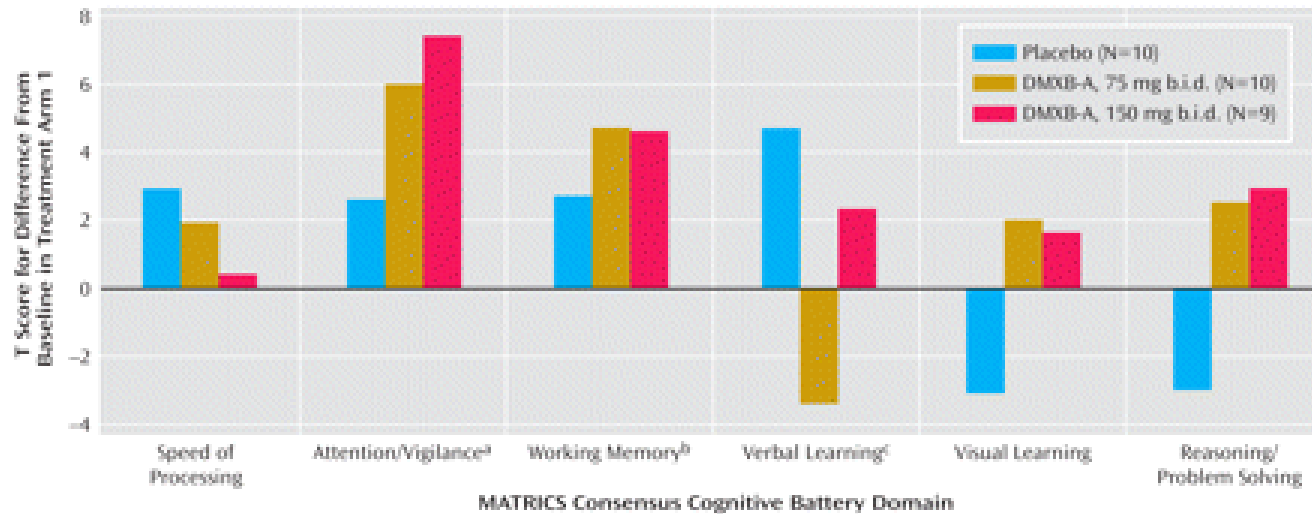
Dopaminergic Homeostasis

Dopamine Synthesis Capacity vs. Turnover



Nicotinic Modulation of Cognitive Performance in Patients with Schizophrenia

DMXB-A effect (Partial α_7 -agonist)



Conclusion

- **High comorbidity between schizophrenia and nicotine dependence**
- **In rodents and primates acute nicotine administration causes elevated brain dopamine levels**
- **In animal models of schizophrenia this effect is pronounced**
- **Improvement of cognitive performance most-likely due to dopaminergic mechanisms**

Conclusion

- Nicotine addicted patients show relatively lower FP binding in striatum
- In patients with schizophrenia at early stages different $D_{2/3}$ receptor-binding pattern: Increased [^{18}F]fallypride binding in striatal and extrastriatal regions
- Dopaminergic regulation in schizophrenia is uncoupled
- Normalization of dopaminergic turn-over may be beneficial to cognitive impairments in schizophrenia

Contributions

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