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Prediction and detection of off-target drug effects on mental health: from neuronal cell models to neuroimaging

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Federal Institute
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and Medical Devices

Disclaimer

This lecture is on regulatory research, and does not imply regulatory guidance

Regulatory research

„… To fill the gaps in scientific needs for the support of regulatory decisions and the minimization of drug-associated risks in the general population“

(German Science Council 2014)

CNS: Target organ and vulnerability site in drug therapy

- Deep compartment
- Blood brain barrier
- Elimination difficult
- Brain local metabolism

→ Severe adverse drug effects

→ off-target activities of metabolites

- BIA 10-2474: off-target effects inhibition of lipid hydrolases within neuronal cells (van Esbroeck et al., Science 2017: 356, 1084-879

Drug effects in the CNS

- Multiple drug targets within the brain
  - H2-receptors
  - D2-receptors
  - Ach-receptors
- May have an effect on brain function:
  - Cognition
  - Emotion
  - Motivation
  - Motor symptoms, movement
  - Sensibility, consciousness, pain
- Modulated
  - by local brain metabolism
  - by drug transporters

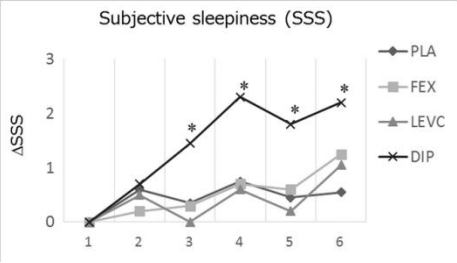
psychiatric

neurological

Off-target effects of drugs in the brain

Antihistamines

- 4-11% of pilot fatalities/accidents in 1990 - 2004 (Aviat Space Environ Med. 2007 May;78(5):514-22)
- Sleepiness



Pla, placebo;
Fex, fexofenadine;
Lev, levocetirizine;
Dip, diphenhydramine

Proton pump inhibitors

Original Investigation

Association of Proton Pump Inhibitors With Risk of Dementia
A Pharmacoepidemiological Claims Data Analysis

Willy Gomm, PhD; Klaus von Holt, MD, PhD; Friederike Thomé, MSc; Karl Broich, MD; Wolfgang Maier, MD; Anne Fink, MSc; Gabriele Doblhammer, PhD; Britta Haenisch, PhD

How to measure side effects in the CNS?

Drug effects on mental health/neural circuits

- Emotional
- Cognitive
- Motivational
- Behavioral phenotypes

Behavioral, neural, and genetic dimensions

Research of drug effects on brain function

Animal model

Exposure to stress/ aversive environment

Morphological changes
e.g., hippocampus

Neurobiology
Behavioral changes
sensitivity to distress,
despair behavior

Human model

Pharmacological effect
Pharmacogenetic modulation

Structural imaging
Size of functional brain structures

Functional Imaging
Behavioral phenotypes
Fear, anxiety
Responsiveness to reward
Working memory
Empathy, facial expression identification

Neurodevelopment

Physical Health

Mental Health

Social Health

Eranet project BrainCYP

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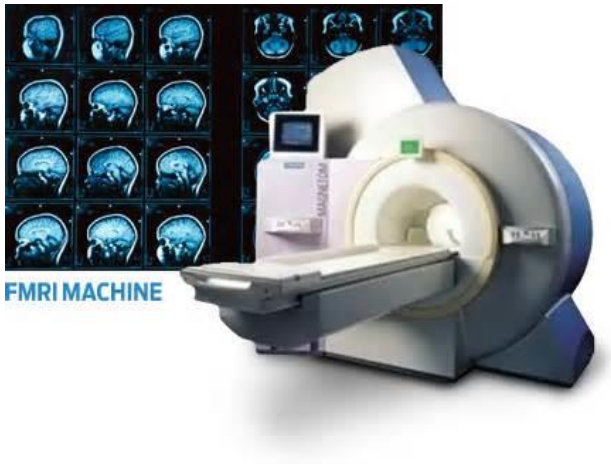
Brain functional imaging paradigm to study pharmacological and pharmacogenetic modulation of psychological phenotypes

- emotional, aversive motivation (mourning pictures/emotional faces)
- motivation, cognition (scrambled sentences)
- appetitive motivation(low-versus-high reward)



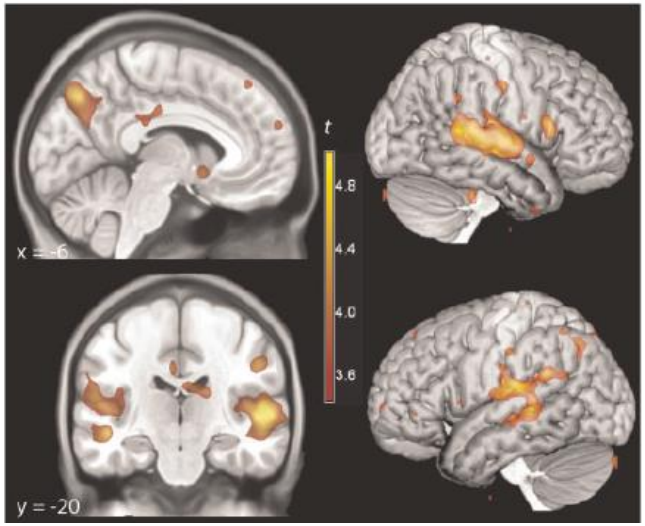
Eranet project BrainCYP

Validation of fMRI paradigms for drug effects

Novel paradigms:

Mourning related drawing versus control drawings

▪



Main contrast: mourning vs Control. The contrast mourning vs control pictures revealed extensive bilateral activations in the posterior superior temporal gyrus that extended deeply in the Sylvian fissure to reach the parietal operculum (Figure 4 and

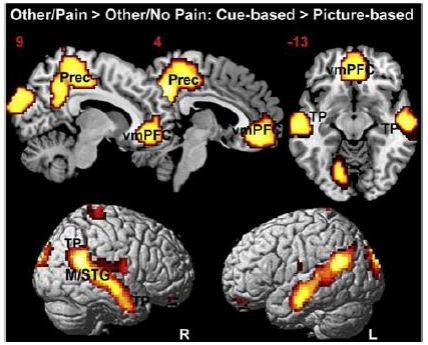


Fig. 4. Higher activation during cue-based than during picture-based studies (Precuneus (Prec), ventral medial Prefrontal Cortex (vmPFC), Medial and Superior Temporal Gyrus (M/STG), Temporo-Parietal Junction (TPJ), and Temporal Pole (TP), other specifications as in Fig. 3).

Empathy for pain :
Posterior network: somatosensory regions centred on the parietal operculum and the superior temporal gyrus (Gazzola et al. 2006; Gazzola and Keysers 2009; Keysers et al. 2010),

Labek et al., Social Cognitive and Affective Neuroscience, 2017, 1303–1313

Eranet project BrainCYP

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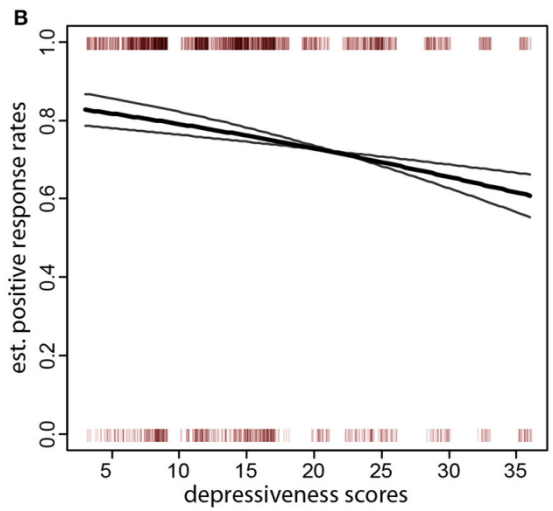
Validation of novel fMRI paradigms:
Scrambled sentences

- latent depressogenic schemas (Wenzlaff 2)
- Example: there is plenty of hope/mourning in life



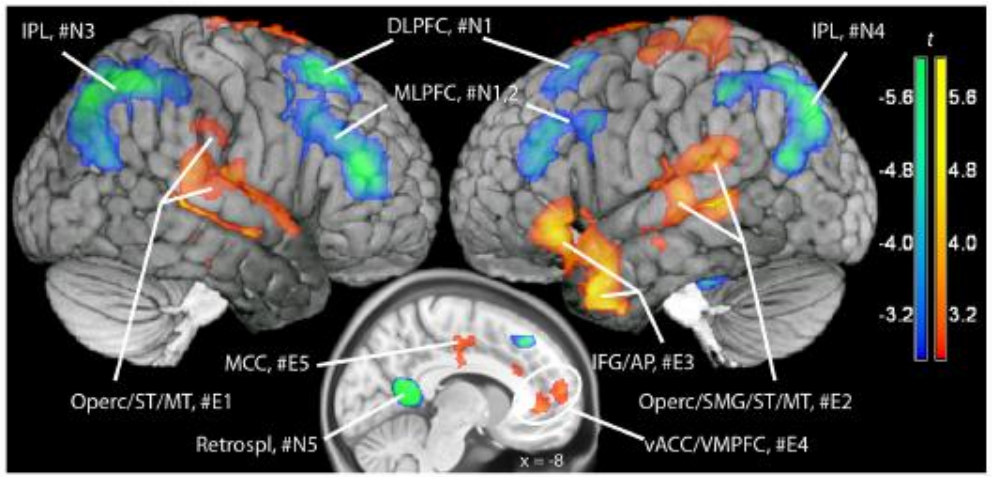


FIGURE 3 | Maps of t statistics obtained in the emotional vs. neutral contrast (in red-yellow) and in the neutral vs. emotional (in blue-green) rendered on a template

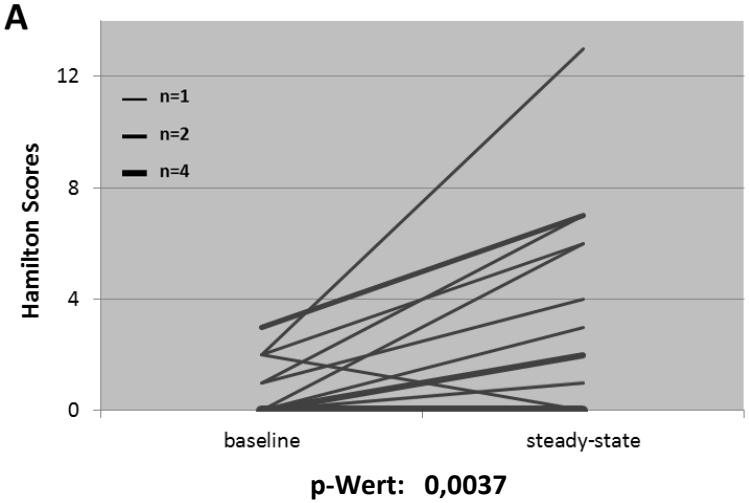
Emotional versus neutral sentences:
shift in brain activation to ventral areas coordinating **motivational and associative processes for spontaneous decisions** (preference values of alternatives)

Viviani et al., Front Psychol. 2018 Jan 9;8:2310.

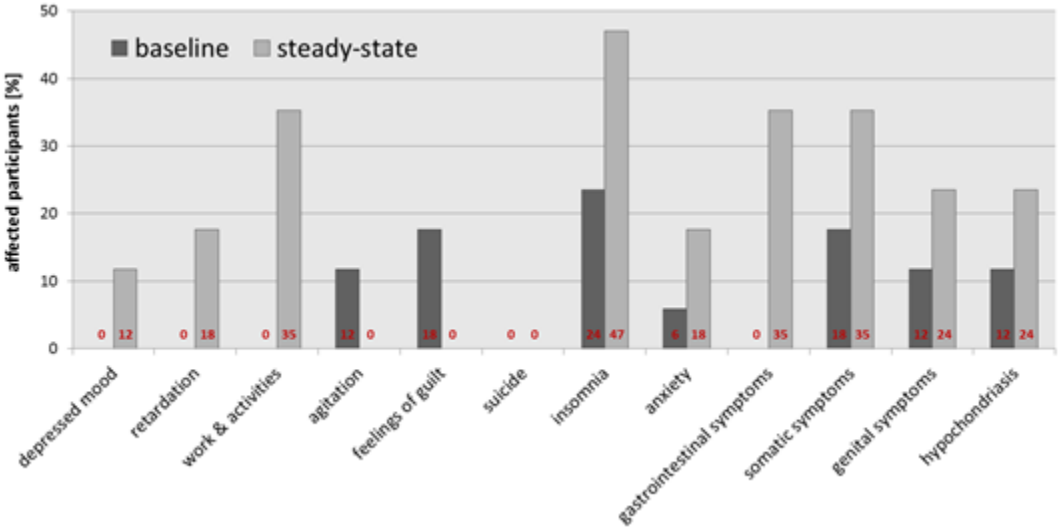
Established fMRI paradigms for measuring off-target drug effects in the brain:

Reward motivation and *Emotional faces* paradigm

Interferon beta (ongoing study): Adverse drug effect: depression?



N=17 healthy volunteers, 9 days of interferon beta

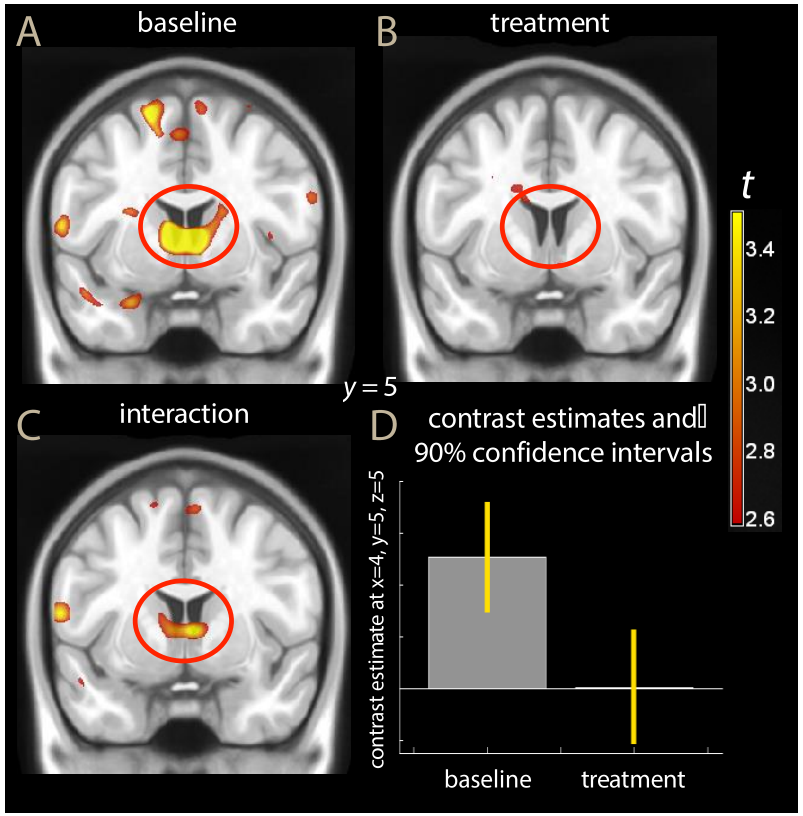


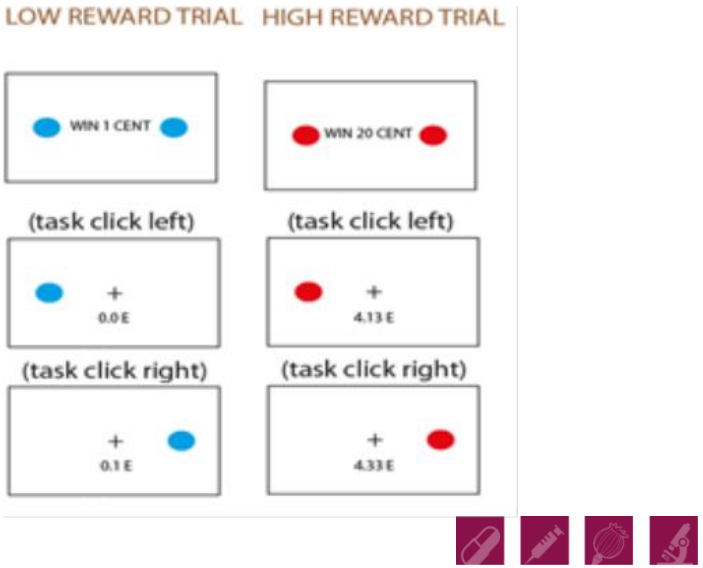
Data on file

Study design: BMC Pharmacol Toxicol. 2015 Sep 22;16:25

Interferon beta:
Adverse drug effect: depression?

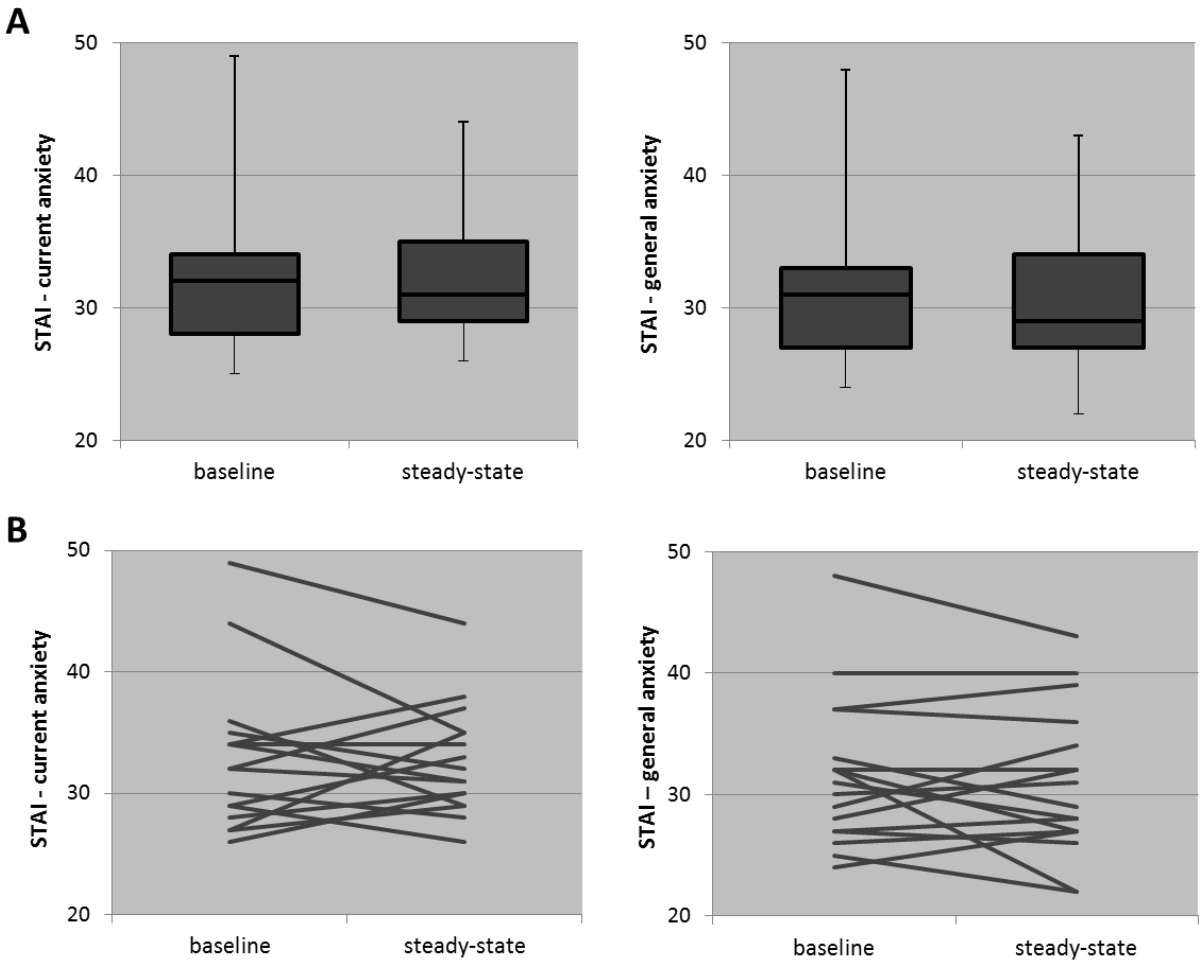
- Low revard versus high reward paradigm in fMRI
- Dopamine related incentive motivation
- Ventral striatum, Nucleus accumbens





Data on file, publication in preparation

Interferon beta:
Anxiety: STAI



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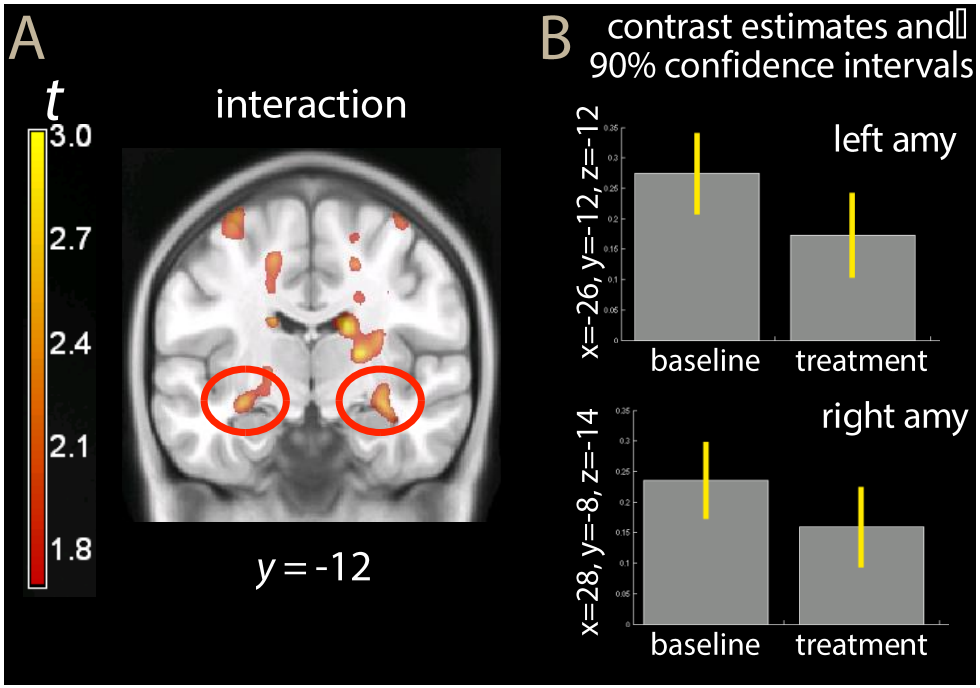
Interferon beta:
No effect in amygdala activation during emotional facial expression paradigm



Negative valence (anxious/depressive phenotype)

No effect of interferon
on amygdala activation

Data on file, publication in preparation

Antidepressant drug side effect: sexual dysfunction

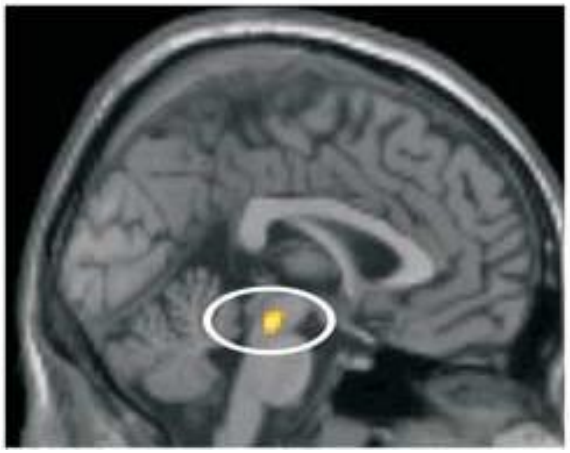
Appetitive motivation fMRI

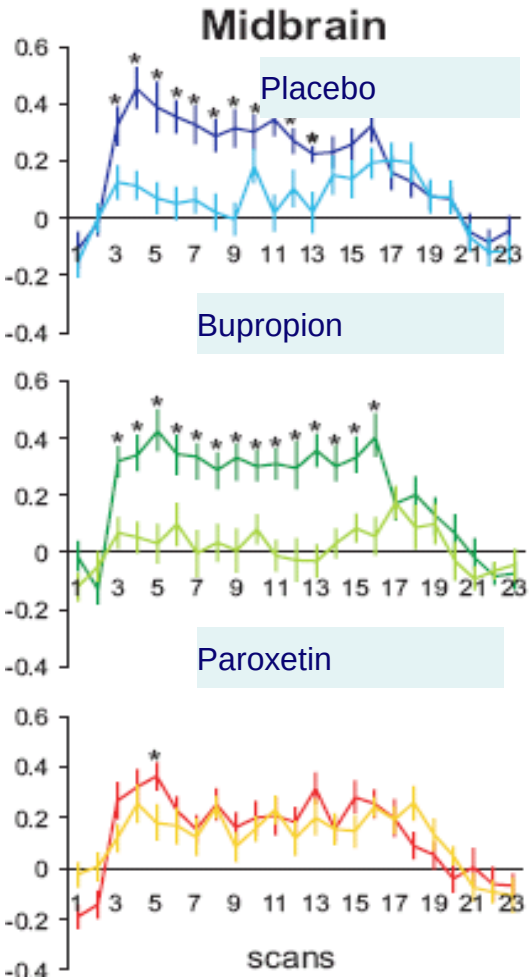
Viewing erotic videos

Modulation of ventral striatal activation by the subjectively perceived sexual intensity of a stimulus (Walter et al, 2008a)

Antidepressants

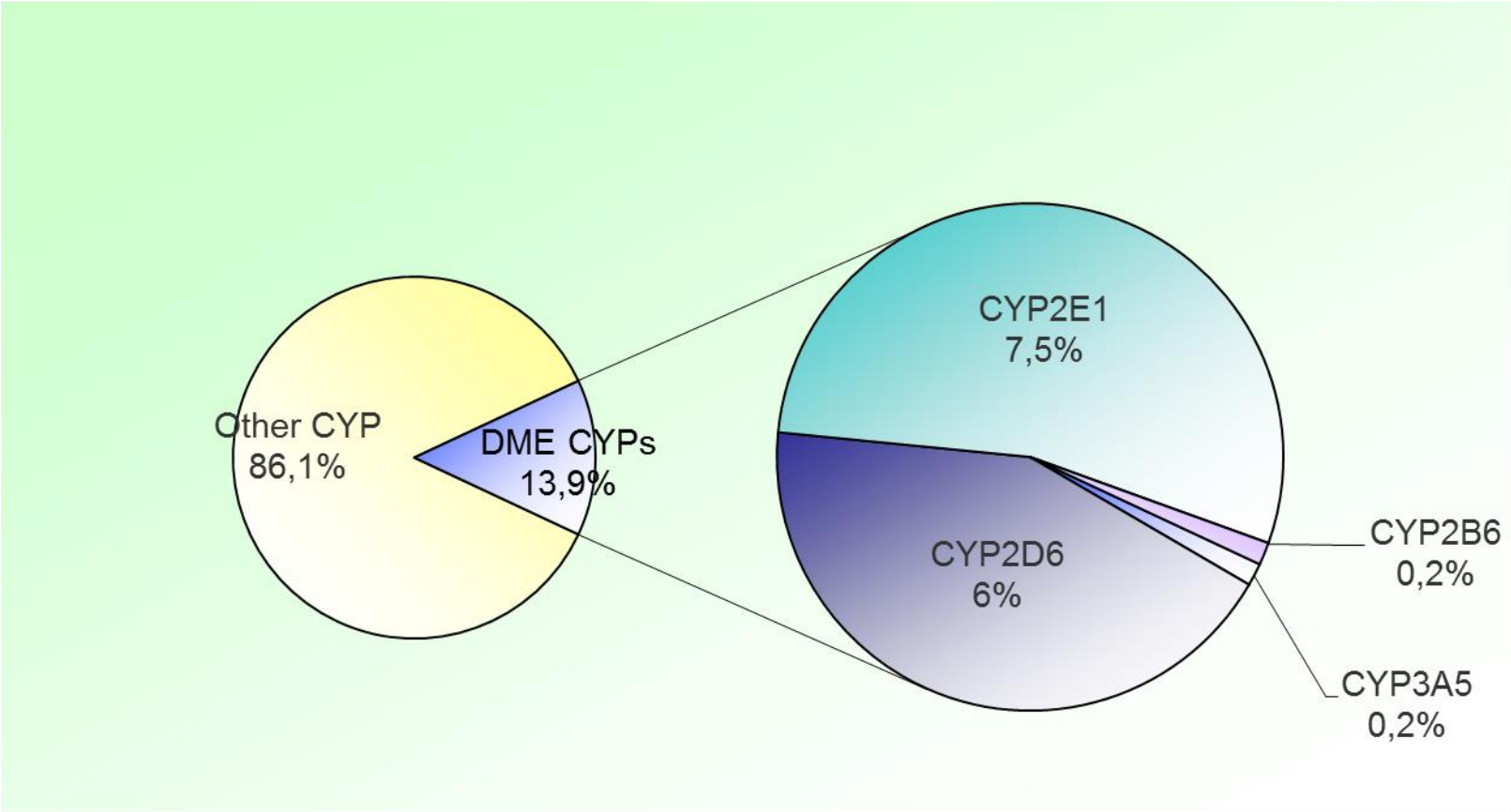
- Paroxetine
- Bupropion
- Placebo





Abler B et al., Neuropsychopharmacology 2011: 36(9):1837-47

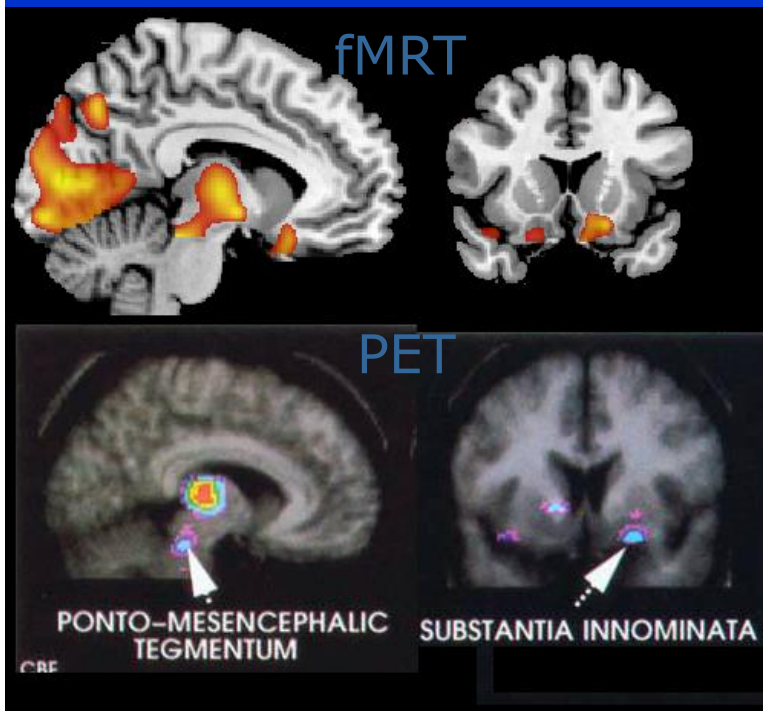
Drug metabolism / CYP expression in the brain:
Active drug metabolites generated within the brain?



Stingl et al., Mol Psychiatry 2013;18(3):273-87.

Drug metabolism in the brain: Functional role of CYP2D6 activity in the brain

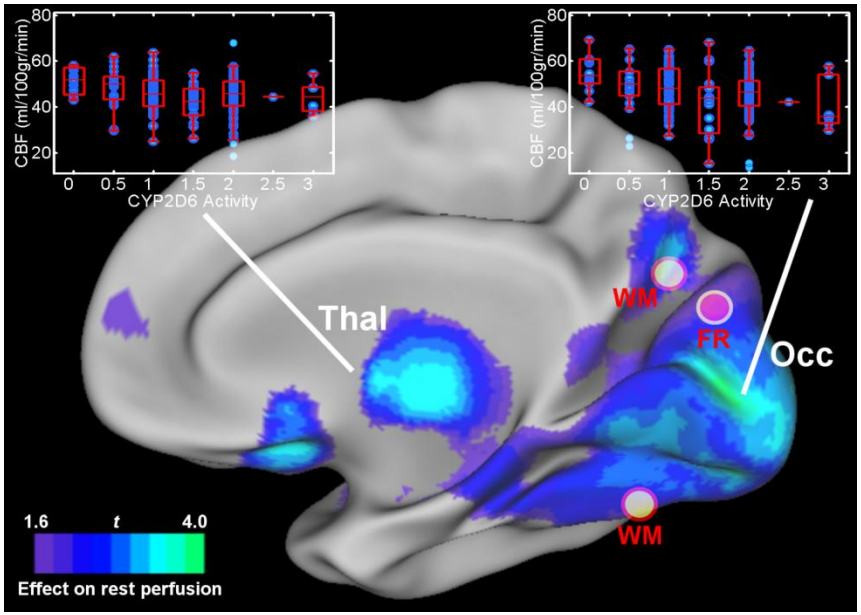
CYP2D6 Genotype and resting brain perfusion



Kirchheiner et al., Mol Psychiatry 2011;16: 333-41

Paus et al., Journal of Cognitive Neuroscience 1997; 9:392-408

Working memory test, Facial expression matching test



Stingl et al., Neuroimage 2012;59(3):2818-23

Role of drug metabolism in the brain:

- active metabolites
- neurodevelopment

- Development of standardized testing systems for drug metabolism in neuronal stem cells
- Pharmacogenetic variability in brain metabolism
- Metabolite profiles of drugs acting in the brain

EFRE.NRW
Investitionen in Wachstum und Beschäftigung

Leitmarktwettbewerb LifeSciences.NRW

EUROPÄISCHE UNION
Investition in unsere Zukunft
Europäischer Fonds für regionale Entwicklung

Titel des Projektes: Standardisierte und integrierte Verfahren zur personalisierten stammzellbasierten Wirkstoffprädiktion mittels reprogrammierter Blutzellen

Kurzbezeichnung: StemCellFactory III

Konsortium Bonn, Aachen: (2017-2019)

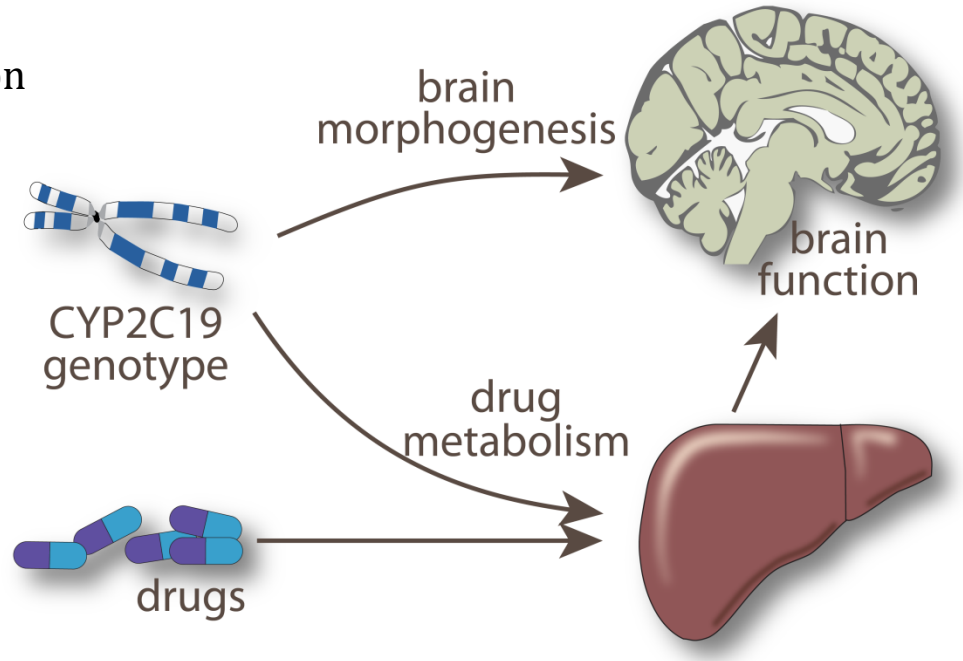
The dual role of CYP enzymes in the brain: Drug metabolism and endogenous neuroregulation

Neurotransmitter
- methoxyphenylethylamine to tyramine to dopamine
- 5-methoxytryptamine into serotonin

Hormones
- progesterone 2ß- and 21-hydroxylation

Endocannabinoids
- Anandamide

Neurotoxins



Stingl, Am J Psychiatry. 2018 May 1;175(5):395-397

Conclusion

- Off-target-drug effects can influence
  - neurodevelopmental origin of psychiatric disease,
  - mental health,
  - mimic or worsen psychiatric diseases
- Drug metabolism in neurons influences inner-brain off-target effects of drugs
- Symptomatology of drug side effects in the brain may be captured by concepts considering neurodevelopmental origins of mental disorders

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