Neuromodulation

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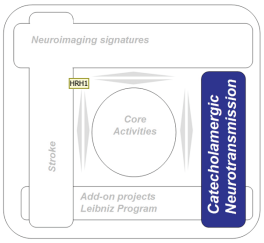

Overview

- New theme in second funding period
- Emerged from successful start-up projects of first funding period
- Focuses on frontal lobe dopaminergic neurotransmission in aging, schizophrenia, and stress.
- Integrates neuropsychiatric research into BNIC

Project	System	Task	State/Disease	Pharmacological Intervention	Genetics
P11	Dopaminergic	Working memory, episodic memory	Aging	D-amphetamine	COMT
P12	Dopaminergic-glutamatergic	Reward expectation	Schizophrenia	Neuroleptics	COMT
P13	Noradrenergic	Emotion regulation	Borderline personality disorder	Yohimbine	
S3 (Add-on)	Dopaminergic	Time discrimination	Attention deficit hyperactivity disorder	Methylphenidate	

Dopamine and Cognitive Aging (P11)

- COMT genotypes differ in rate of dopamine (DA) degradation: val/val > val/met > met met
- Aging and COMT val genotype are associated with less DA signaling, lower cognitive performance, and more diffuse brain activation patterns during cognitive processing
- There is an inverted U-shaped relation of DA signaling to cognitive and brain functions

Goals

- Examine how aging and COMT genotype interact regarding cognitive and brain function
- Clarify the role of the diffuse brain activation patterns often shown by older adults during cognitive processing (i.e., functional recruitment vs. deficient neuromodulation)
- Test the inverted U-shape model by determining whether administration of a DA agonist results in more efficient cognitive and brain responses for certain persons (i.e., old-val/val) and less efficient responses for others (i.e., young-met/met)
- Include the effects of COMT genotype and DA agonists in extant computational models

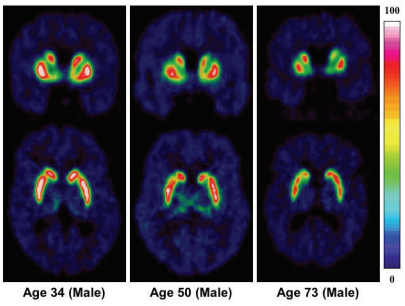

Fig 1: DA transporter binding through the caudate-putamen level across adult age (Erixon-Lindroth et al., 2005, *Psychiatr Res Neuroimag*

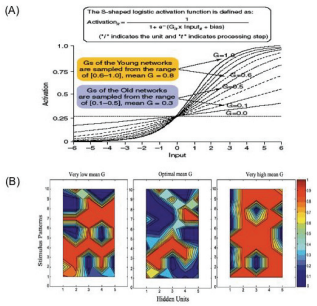

Fig 2: A. Modeling DA modulation by the Gain parameter of the sigmoid function. **B.** U-function of non-optimal Gain modulation and diffuse activation patterns (Li, Lindenberger, & Sikström, 2001, *TICS*).

Dopamine-Glutamate Interactions in Schizophrenia (P12)

- Prefrontal cortical (PFC) function is impaired in schizophrenia (Gallinat et al. 2002, *Neuroimage*; Gallinat et al. 2003, *Biol Psychiatr*) and dysfunctional interaction with medio-temporal structures is a current target of imaging studies in these patients
- Genetic variations in dopamine and serotonin systems have been associated with dysfunctional fronto-temporal as well as dopamine-glutamate interactions (Heinz et al, *Nat Neurosci*; Fig. 3 & 4).

Goal: To better understand fronto-temporal and dopamine-glutamate interaction in schizophrenia during reward processing.

1. Examine effect of frontal glutamate concentration (MRS) and BOLD contrast in the nucleus accumbens (fMRI) during reward processing.
2. Explore dysfunctional interaction in schizophrenic patients and possible causes in DTI abnormalities and effects on negative symptomatology and cognitive deficits.

Multimodal imaging will promote future analytical methods (feature extraction, support vector machines) of the Computational Neuroscience Center in Berlin and help to integrate cerebral function and neurotransmission in schizophrenia research.

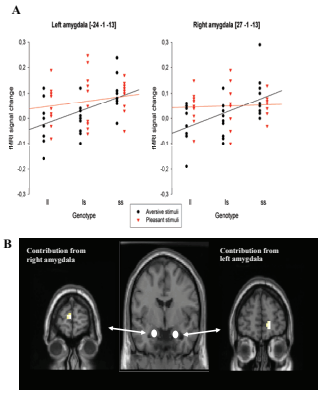

Fig. 3: A: 5-HTT genotype affects amygdala activation during aversive (black) and appetitive (red) stimuli as well as the amygdala-frontal lobe interaction (**B**).Heinz et al, *Nat Neurosci in press.*

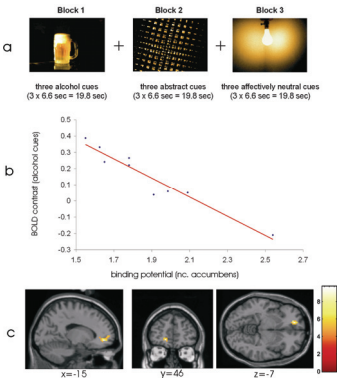

Fig. 4: Dopamine binding potential correlates with frontal lobe BOLD contrast. Heinz et al, *Nat Neurosci in press.*

Stress-Induced Neuromodulation in Prefrontal Cortex (P13)

- Prefrontal cortical (PFC) function is influenced by acute and chronic stress.
- Several psychiatric diseases show severe impairment of PFC functioning under stress, e.g. emotional regulation processes are dysfunctional in patients with borderline personality disorder (BPD).

Goal: To better understand how stress influences emotion regulation at behavioral and cortical levels in healthy controls and patients with BPD.

- Pharmacological stress induction with α2-adrenergic antagonist yohimbine → investigate its effect on emotion regulation at the behavioral and cortical level.
- Examine behavioral effects of pharmacologically induced stress during emotion regulation using low dose and high dose yohimbine as well as placebo.
- Determine cerebral correlates of the effect of pharmacologically-induced stress on emotion regulation using fMRI.
- Apply protocol to a sample of in-patients with BPD.
- Results will help to understand detrimental effects of stress in psychiatric diseases and may foster new approaches in pharmacological treatment, especially in psychiatric diseases due to emotional dysfunction such as BPD.

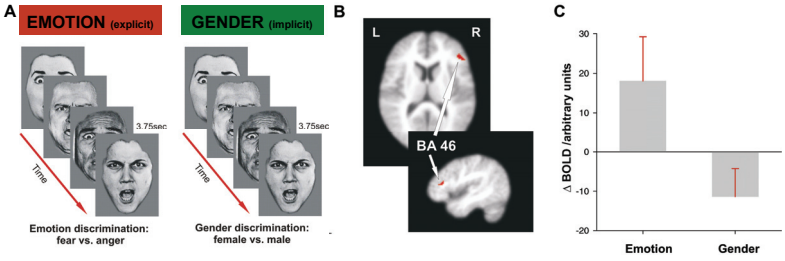

Fig. 5: Task and preliminary data. A.Task: Either the emotion or gender of visually presented faces or the shape of a geometrical figure (control, not shown) had to be judged. **B & C**. Greater activation in right DLPFC during emotion relative to gender discrimination.