Imaging in CNS Translational Drug Research

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Contents:

• translational neuroscience in Leiden
• CNS homology among species
• translational neuroimaging technologies:
  – EEG
  – PET
  – MRI
• future developments
  – methodological
  – organizational
What is Translational Neuroscience?
Translational Drug Development: ‘from bench to bedside and back’

• Functional homology
• Disease models
• Pharmacological studies
• ‘-omics and -imaging’
Homology Between Species

• neuroanatomical evolution
• neuroimaging
• preserved neurobehavioural systems
NeuroImaging Techniques as Biomarkers

'A quantitative measure that is on the causal path between drug administration and effect’
(EU COST-B Biomarker Working Party, Danhof, 2005)

'A tool that answers a drug development question’
(AGAH, Van Gerven, 2011)
Leiden Pharmaco-Imaging Collaborations
Preserved Cerebral Cortex: EEG in Animals and Humans

- REM Sleep reduction
- Spikes-and-Waves
- EEG Beta Power
- antidepressants
- antiepileptics
- GABAergic anxiolytics
Drug-Class Specificity of EEG-Effects: Benzodiazepine- and Neuroleptic-induced EEG-profiles


Epilepsy Models in Animals and Humans: EEG network analysis
Epilepsy Models in Animals and Humans: Spasms in Rats, Photosensitivity in Patients


PET in Animals and Humans
Fast-Dissociating D2-Antagonist for Schizophrenia

- Demonstration of fast-D2-receptor dissociation in healthy volunteers, however, uncertain dose estimates by raclopride PET

- Estimation of PD-equipotent dose of regular vs fast dissociating D2-antagonists in healthy volunteers

- Confirmation of clinical efficacy in PD-predicted dose range
HiRes Animal Research MRIs

fMRI

T1/T2

7.0 - 9.4 - 17.6 T

molecular (amyloid) imaging
HiRes Human Research MRIs

1.5 - 3.0 - 7.0 T

T1/T2

ASL

fMRI

RS-fMRI

DWI

MRS
Drug-induced regional BOLD-signal changes

- modified neuronal activity with intact neurovascular coupling
- modified metabolic activity
- modified local vascular tone (CBF/CBV)
- modified systemic → cerebral flow/volume

Direct pharmaco-MRI of acute drug action

- SSRI citalopram infusion in healthy subjects
- Acute changes in areas implicated in depression:
  - left anterior cingulate
  - caudate
  - amygdala
  - striatum
  - thalamus
‘Traditional’ Task-Induced fMRI

Fox, M. D. and Raichle, M. E. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature Reviews Neuroscience 8(9), 700-711. 2007
Acute SSRI-effects on ‘Emotional Faces’ fMRI


Rawlings NB, Norbury R, Cowen PJ, Harmer CJ. A single dose of mirtazapine modulates neural responses to emotional faces in healthy people. Psychopharmacology (Berl) 2010;212:625-34
‘Resting State’ fMRI

Fox, M. D. and Raichle, M. E. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature Reviews Neuroscience 8(9), 700-711. 2007
Default-Mode Network in Rat Resting State fMRI

man 3.0T awake eyes closed  mouse 7.0T isoflurane

NARI/SSRI-effects on ‘Task-Induced’ vs ‘seed-based Resting State’ fMRI


SSRI-effects on ‘seed-based-’ vs ‘whole brain Resting State’ fMRI

**whole-brain RS-fMRI**

**emotional faces fMRI**

**seed-based RS-fMRI**

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**Bernadet Klaassens, Helen van Gorsel, Serge Rombouts, Joop van Gerven, Brad Wyman**

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LUMC/CHDR Brain Connectivity Studies

- sertraline
- citalopram
- galanthamine
- levodopa
- haloperidol
- morphine
- ethanol
- cannabis
- ketamine
Dopamine Modulation: ‘effect-response relations’

Cannabinoid Modulation: ‘dose-response relations’

Sensorimotor network expansion by psychomimetic drugs

Δ9-tetrahydrocannabinol, ketamine, ethanol, morphine

Subjective effects of ethanol, morphine, Δ9-tetrahydrocannabinol and ketamine following a pharmacological challenge are related to functional brain connectivity. Hum Brain Mapp 2013 (submitted)
Future Developments: methodology

• Resting state pharmaco-MRI in laboratory animals
  – stable non-interfering anesthaesia
  – medetomendine effects/interactions in animals/humans

• Quantification of resting state fMRI signals
  – expansion/intensity of network activity
  – PK/PD-analysis RS pharmaco-MRI

• Separation of BOLD-signal components
  – neuronal activity/O2 consumption/flow/volume
  – arterial spin-labeling ASL
  – peripheral/central vasoactive congeners

• Resting state pharmaco-MRI library
  – drugs, effects, diseases
  – methodological properties, relationships
Future Developments: organization

• Dedicated 3T-MRI facility for drug research
  – European Population Imaging Infrastructure
    • Mark van Buchem

• Collaborative functional MRI network
  – Oxford Centre for Functional MRI of the Brain (FMRIB)
    • Stephen Smith
    • Christian Beckman
  – Pfizer Molecular Medicine
    • Brad Wyman
  – others