PLEASE NOTE: *This trial has been registered retrospectively.*

Trial Description

Title

PFC-HC coupling in schizophrenia and related polymorphisms in working memory

Trial Acronym

[---]*

URL of the trial

http://www.bccn-heidelberg-mannheim.de/pub/projectsad_project_for.php?a=03000008200000000000000000

Brief Summary in Lay Language

This project will be conducted within the framework of the recently founded Bernstein Center for Computational Neuroscience Heidelberg-Mannheim. The general goal is to characterize the influence of genetic risk polymorphisms for psychiatric conditions on large-scale brain networks and associated cognitive processes. Our approach is both interdisciplinary and translational, involving genetics, modeling und imaging techniques.
Within this project, functional imaging data (fMRI) of a large sample of healthy subjects is collected during execution of paradigms that involve higher cognitive functions (e.g. working memory, executive functions, spatial memory etc.). Cognitive functions within these domains are strongly impaired in patients suffering from schizophrenia.
In order to characterize systematic differences of large-scale brain networks between schizophrenic patients and healthy subjects, we will also include schizophrenic patients in our study. The main target regions are the prefrontal cortex, the hippocampus and their dopaminergic innervation. These structures have been implicated in abovementioned cognitive processes and altered function of both brain regions as well as their connectivity have been proposed to play a major role in the pathophysiology of schizophrenia.
Polymorphisms in several risk genes will be characterized in all subjects. Genetic information will be combined with functional imaging data to investigate the influence of these genes on both brain activation and cognition. These effects will be captured in mathematical models and predictions from these models provide the basis for future experiments that aim at a better understanding of pathophysiological mechanisms.

Brief Summary in Scientific Language

We have shown that abnormal connectivity of hippocampus/entorhinal cortex (HC) and lateral prefrontal cortex (PFC) characterize patients with schizophrenia and carriers of risk allele for the disease. These brain regions are also major contributors to a profound change in network topology in schizophrenia. We have

demonstrated that global network connectivity shapes the dynamical repertoire of brain functions and predicts cognitive performance during working memory. The functional and computational implications of abnormal HC-PFC coupling are, however, still incompletely understood. Here, we use neuroimaging in tight relation to computational projects (Prof. Dr. Daniel Durstewitz) to reach a precise neural systems level characterization of effective connectivity during working memory in schizophrenia and risk gene carriers. We will extend our previous work on functional and effective connectivity during working memory to assess directionality and temporal dynamics of PFC-HC interactions and to quantify the regional contribution of this interaction to the connectome. These experimentally derived functional connectivity dynamics will be compared to those obtained from simulated BOLD signals in models under similar conditions to gain insight into the biophysical processes and dynamics underlying the experimental observations at this macroscopic level, and into crucial (gene-dependent) parameter regimes governing these PFC-HC interactions. We will study the n-back task and a novel working memory task that parallels the 8-arm radial maze used in rodent studies.

Organizational Data

- DRKS-ID: **DRKS00004290**
- Date of Registration in DRKS: **2012/11/07**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **2011-206N-MA , Medizinische Ethik-Kommission II Medizinische Fakultät Mannheim der Universität Heidelberg**

Secondary IDs

Health condition or Problem studied

- ICD10: **F20.0 - Paranoid schizophrenia**

Interventions/Observational Groups

- Arm 1: **Patients**
  All subjects are screened for possible exclusion criteria. Subjects that gave their informed consent will undergo neuropsychological testing. The investigated domains include attention, memory, executive functions, IQ as well as personality traits. Important control variables including blood pressure depressive symptoms, nicotine and alcohol use as well as sociodemographic factors are collected. Symptom severity in patients is evaluated using scales and in a clinical interview.

Functional MR imaging is conducted while subjects complete several paradigms. These tasks probe higher cognitive functions including explicit/implicit memory, cognitive flexibility as well as working memory.

All subjects are asked to provide blood samples for molecular genetic studies.

- Arm 2: **Healthy Controls**
  All subjects are screened for possible exclusion criteria. Subjects that gave their informed consent will undergo neuropsychological testing. The investigated domains include attention, memory, executive functions, IQ as well as personality traits. Important control variables including blood pressure depressive symptoms, nicotine and alcohol use as well as sociodemographic factors are collected. Symptom severity in patients is evaluated using scales and in a clinical interview.

  Functional MR imaging is conducted while subjects complete several paradigms. These tasks probe higher cognitive functions including explicit/implicit memory, cognitive flexibility as well as working memory.

  All subjects are asked to provide blood samples for molecular genetic studies.

Characteristics

- Study Type: **Non-interventional**
- Study Type Non-Interventional: **Other**
- Allocation: **Non-randomized controlled trial**
- Blinding: **Open (masking not used)**
- Who is blinded: **[---]***
- Control: **Other**
- Purpose: **Basic research/physiological study**
- Assignment: **Parallel**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

• Characterization of task-related BOLD activation in healthy subjects and patients using both univariate (statistical parametric mapping) and multivariate methods („machine learning“).

• Evaluation of prefrontal-hippocampal connectivity during working memory processes.
• Modulation of both activity and connectivity patterns by psychiatric risk polymorphisms.

Secondary Outcome

- **Comparison of imaging data with biophysical models (cooperation with Prof. Dr. Daniel Durstewitz) to gain a better mechanistic understanding of underlying (patho)physiological processes**
- **Development of multivariate statistical methods that can be used with functional imaging data**
- **Correlation of neuropsychological and imaging data**

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Mannheim und Heidelberg**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2012/01/17**
- Target Sample Size: **220**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **50 Years**

Additional Inclusion Criteria

All subjects:

•Adequate proficiency in German language

•Ability to understand the study protocol and give informed consent

Exclusion criteria

- **subjects with a psychiatric condition (healthy controls), acute worsening of symptoms or additional psychiatric condition (patients)**
- **presentation with a severe neurological disorder**
- **major medical conditions e.g. renal failure, hepatic cirrhosis**
- **pregnancy**
- **metal implants**
- **tatoos covering head or neck**
- **claustrophobia**
- **substance abuse (excluding nicotine and caffeine)**
- **arterial hypertension**
- **diabetes**

Addresses

■ **Primary Sponsor**

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Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

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Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*
**** This entry means that data is not displayed due to insufficient data privacy clearing.*