

CNS drug discovery at Boehringer Ingelheim

A fresh approach to neuropsychiatric diseases

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Boehringer Ingelheim in Brief



- **Family-owned global corporation** dedicated to *Value through Innovation* since 1885
- **Focus on Human Pharmaceuticals, Animal Health and Biopharmaceutical Contract Manufacturing**
- Around **45,700 employees** worldwide
 - ~8000 staff in research, development and medicine
- **Four major Human Pharma R&D sites** worldwide
 - Germany, USA, Austria, Japan
- 2016: **15.9 billion EUR Net Sales** (+7.3%)
 - Thereof 12 billion EUR in Human Pharma
- **Strong commitment** to R&D investment
 - 3.1 billion EUR (+3.6%) in 2016

Partnering with Boehringer Ingelheim



- Innovation is inscribed in our Company vision “**Value through Innovation**”
- A **track record of innovation** from our own research portfolio as well as from projects with our partners
- A **progressive research strategy** positions us for the future of healthcare
- **Increased emphasis on external innovation** allows us to incubate the most creative ideas and pioneer emerging fields of medicine
- **Significant investment** in early-science collaborations

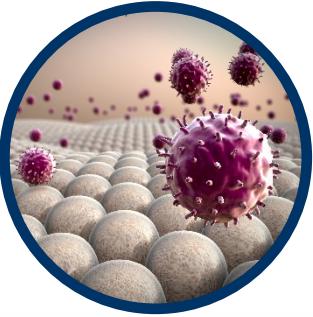
Our Partnering Focus



CardioMetabolic
Diseases



Central Nervous
System Diseases



Immunology



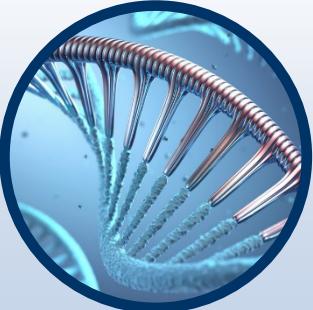
Oncology & Cancer
Immunology



Respiratory Diseases



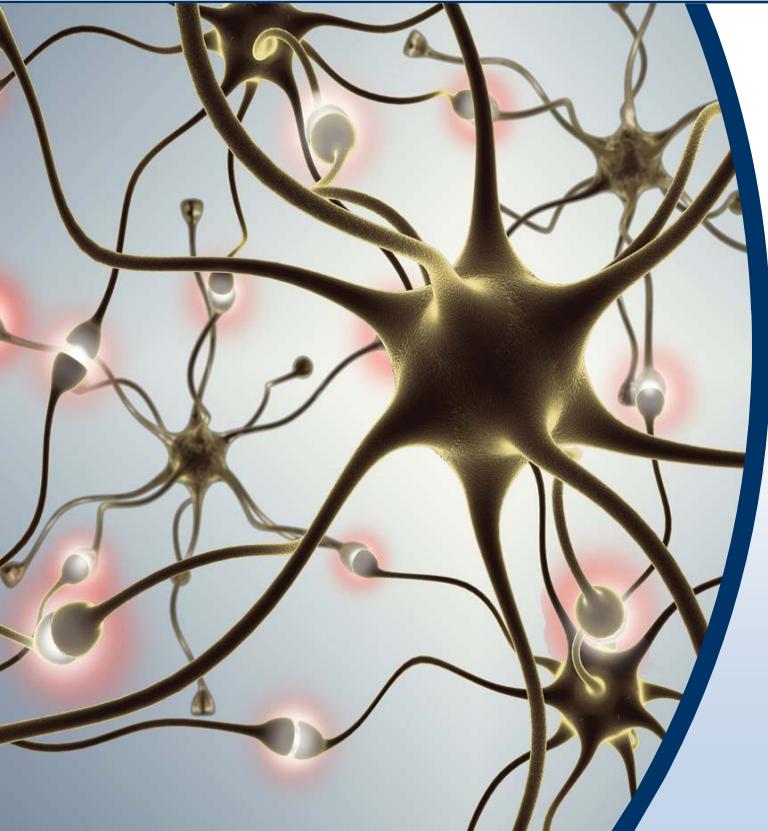
Research Beyond
Borders



Technologies

For more information please visit:
<http://partnering.boehringer-ingelheim.com>

Our CNS partnering focus



- **Neuropsychiatric disorders**, including (but not limited to)
 - **Alzheimer's disease**: cognitive impairment and other neuropsychiatric symptoms
 - **Schizophrenia**: negative symptoms and/or cognitive impairment
 - **Depression**: treatment-resistant depression
 - **Impulsivity disorders** (incl. substance use, obsessive-compulsive, and borderline personality disorder)
- **Specific priorities:**
 - Novel approaches to specifically modulate maladaptive neural circuits/networks as the root cause of various neuropsychiatric symptoms
 - Quantifiable biomarkers
- **Complementary non-drug approaches** (e.g. digital therapeutics)

Working Together in Central Nervous System Diseases

Collaborations with academia and industry advance our pursuit of novel therapeutic approaches to address unmet needs across a range of neuropsychiatric disorders

- Partnering with **Arena Pharmaceuticals** to advance research in schizophrenia by identifying drug candidates targeting a G protein-coupled receptor
- Exploring new therapeutic concepts in CNS diseases with **Autifony** with the aim of accelerating progress towards new medicines in areas of high medical need
- Collaborating with **Hydra Biosciences** on its small-molecule TRPC4/5 inhibitor program
- Working together with **Saniona** to identify compounds that could be capable of restoring brain network activity in patients with schizophrenia



Discovery Research

Pre-clinical development

Clinical development

Regulatory approval/
Phase IV

Visual does not necessarily reflect the stage of development for the partnership highlighted

Pitfalls in Neuroscience

Possible reasons for clinical trial failure and project discontinuation

- Wrong target
 - Lack of solid biological data demonstrating clear role of the molecular target in the underlying pathophysiology
 - Poor predictive validity of animal models used in early phases of CNS drug development
- Wrong dose
 - Inadequate target occupancy over the duration of the trial
- Insufficient safety profile
- Trial design and trial conduct (slow recruitment, high placebo response, ...)
- Heterogeneity of the targeted patient population
 - Different stages of disease progression
 - Different symptom domains impacted
 - Inappropriate clinical scales used

Strategies to de-risk neuroscience drug development

- Improve robustness of preclinical efficacy data from animal models (particularly behavioral models) ...



Lacking quality in research: Is behavioral neuroscience affected more than other areas of biomedical science?

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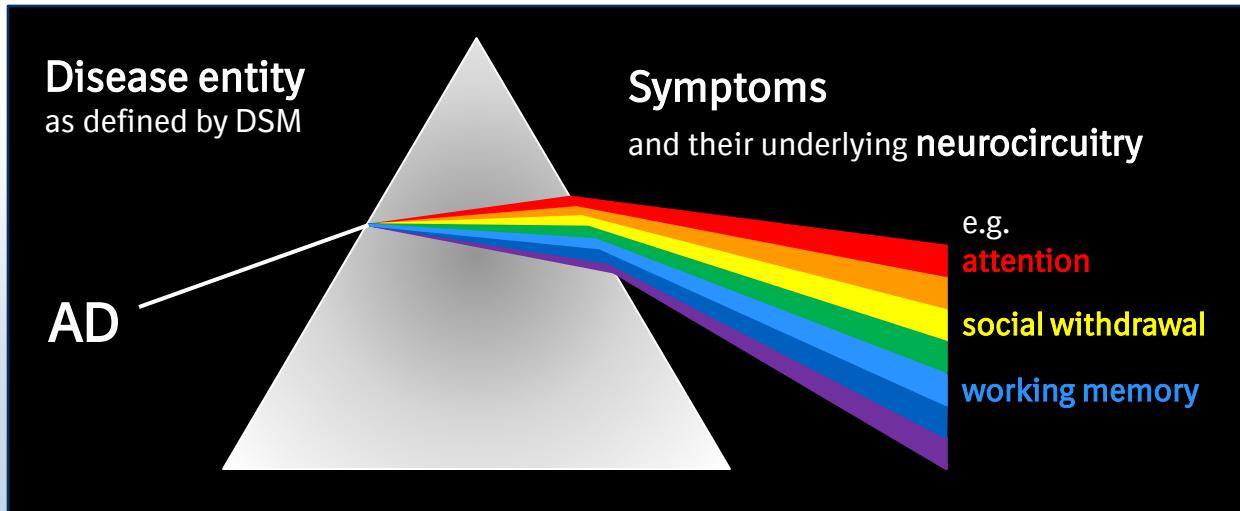
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^cJanssen Research & Development, Beerse, Belgium

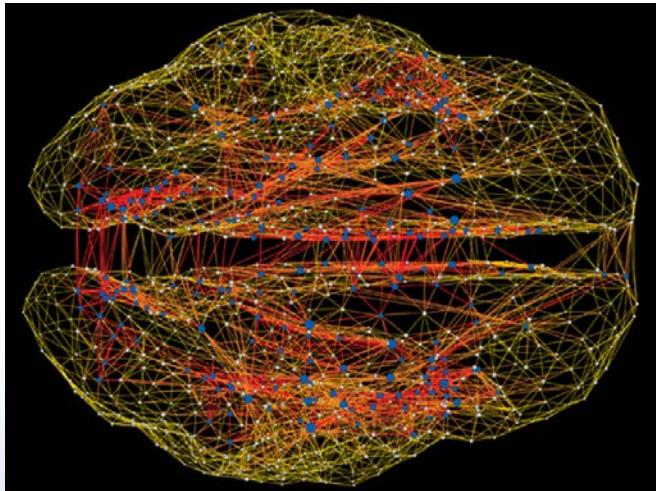
- Use of **biomarkers with good translatability** (incl. back-translation human → animal model), e.g. EEG measurement of standard tone event-related potentials (ERP) in rats and humans
- In early **clinical studies**, ensure adequate dose and **target engagement in the brain**
 - Exposure at the site of action over the desired period of time, based on established preclinical PK-PD relationship, and proven target engagement shown e.g. by PET ligand binding)
 - Expression of pharmacological activity in keeping with target biology (PD biomarker)

Strategies to de-risk neuroscience drug development

- Employ a **neurocircuitry-based precision medicine approach** inspired by the NIMH “Research Domain Criteria (RDoC)” initiative
 - ⇒ Reorientation of the R&D focus in neuropsychiatry:



Neurocircuitry-based precision medicine approach



Human connectome (courtesy of M.P. van den Heuvel)

- Specific neural circuits/networks subserve specific brain functions (e.g. attention, working memory, ...)
- Malfunction of a specific circuit or neural network is responsible for the occurrence of a specific cognitive and/or behavioral symptom



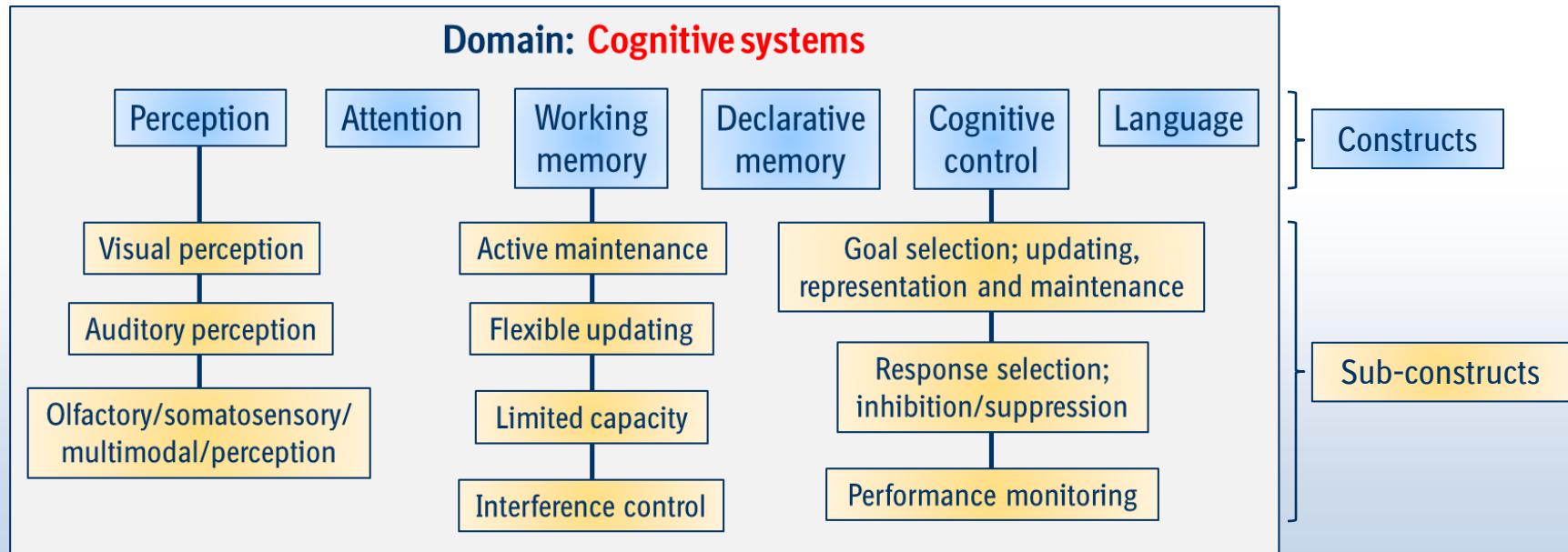
Paradigm shift:

Neuropsychiatric diseases (such as AD) are reconsidered as “syndromes” of disrupted neurocircuitry and the associated specific symptoms

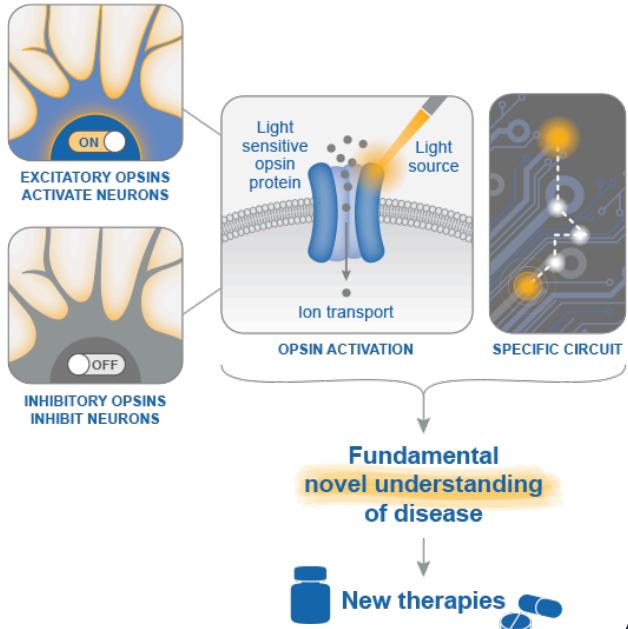
- Different patients within one diagnostic (DSM) category can show different neural circuit impairments and associated symptoms ⇒ **Patient stratification based on quantifiable biomarker(s)**
- The identical neural circuit impairment & associated symptom can occur across different diseases ⇒ **Disease-agnostic circuit/symptom-focused precision medicine approach**

Neurocircuitry-based precision medicine approach (RDoC concept)

- RDoC concept defines five larger domains, including the domain “Cognitive Symptoms”:



Partnerships in Central Nervous System Diseases



Creating a partnership culture for shared success

- Partnering with Circuit Therapeutics to discover new ways of treating brain disorders using Circuit's innovative 'optogenetics' technology

“The innovative and ambitious vision and passion of Boehringer Ingelheim to make a difference in the area of neuropsychiatric disease treatments, combined with Circuit's innovative technologies, make an ideal partnership. We look forward to a highly productive research collaboration that will provide transformational drugs to impact patients' lives.”

Fred Moll, Chairman of Circuit Therapeutics



Outlook

- Dementia drug discovery and development – despite numerous setbacks – remains an important area for Pharma:
 - **Vast unmet medical need** for better treatments for cognitive impairment and many other neuropsychiatric symptoms across a wide range of CNS diseases
 - The very significant **socioeconomic implications** have made dementia a **priority on the public agenda**, leading to an overall more favorable regulatory and market access environment
 - Great strides continue to be made in **understanding the disease biology and diagnosis of dementia**
 - Increased use of **translational medicine** approaches will allow us to obtain signs of drug action and efficacy in early phases of clinical development ⇒ BI “**Proof of Clinical Principle**” approach

Building upon the scientific advances in the field, Boehringer Ingelheim remains committed to the discovery and development of new therapeutic concepts for the treatment of dementia and other neuropsychiatric diseases