Impact Objectives

• Integrate the fragmented research efforts on alcoholism across leading laboratories and clinics in Europe, and combine this with leading expertise in mathematical modelling

• Identify brain connectome alterations that can point to novel alcoholism treatments, and biomarkers that are predictive of clinical efficacy

Order from disorder: a new research network for alcoholism

Professor Dr Wolfgang Sommer is leading a systems medicine-based project that will hopefully yield greater understanding of the brain mechanisms involved in alcohol use disorders, and how such conditions can be treated

Can you explain the current state of knowledge surrounding alcohol addiction?

The urgency to understand more about the changes in the brains of alcohol addicts and to find effective treatments is obvious. Considerable research efforts have been made all over the world and led to increased understanding of the psychological and neurobiological processes that underlie addictive disorders. In turn, there has been substantial enthusiasm about the prospect of developing novel, mechanism based therapies. So far, these prospects have not played out, indicating that the translation of scientific knowledge into the clinical praxis of addiction therapy is not easy. While this translational gap has complex causes, we think that one important limitation of the current neurobiological view on alcohol addiction is the focus on only a few processes and brain regions, albeit the broad systemic actions of alcohol are commonly known. Adopting a systems-oriented approach, one that centrally integrates into the analytical method the interactions and dynamics of many neurobiological and other important factors involved may be helpful. By such an approach, a better understanding of the trajectories into alcohol addiction and hence for defining new treatments may be obtained.

With that in mind, how is your Systems Biology of Alcohol Addiction (SyBil-AA) project contributing to the search for better treatments?

Within the SyBil-AA project we address this problem by adopting a global perspective on brain network organisation – called the connectome – and by making use of mathematical and network theoretical methods. These advanced computational tools will help us to properly describe the dynamics of brain networks in the addicted state, and to compare these with healthy brains. We can then build predictive models about the effects of therapeutic interventions, and generate new hypotheses for testing in animal models and humans.

How are you collecting the data upon which you are building these predictive models?

The data on which we will build predictive models of ‘relapse-prone’ states of the brain connectome come from magnetic resonance imaging (MRI). This method is widely employed in basic and clinical research to map both the functional and structural organisation of the brain. Hence, MRI is principally well suited to obtaining a global view of brain activity. MRI information from humans and laboratory animals is complemented by electrophysiology and neurochemical data.

Who are the researchers that make up this ambitious project?

All the principal investigators (see Project Insights) are internationally well-recognised experts in their own fields, such as basic or computational neuroscience, complex mathematics and network science, as well as clinical scientists. Among our highly interdisciplinary collaboration, we have leading experts on animal models of alcoholism, and the most established clinical alcohol researchers in Europe, as well as several young teams with outstanding expertise in systems biology and network science. Importantly, many of the systems biologists are newly coming to the field of alcoholism.

Can you explain the translational approach based on clinical studies and animal experiments you are employing?

The principal idea of SyBil-AA follows a logical flow of information that starts from observations in healthy and pathological populations (humans and animal models), which provide the basis for mathematical modelling of the state and function of brain networks underlying the different phenotypes (alcohol use disorders vs. healthy). Model predictions will then be subjected to experimental validation in animals and also humans. Iteration of this sequence will lead to model refinement and optimisation, thereby increasing the predictive power of the models. Ultimately, we will be able to make inferences about potential therapeutic strategies.
Solving Europe’s alcohol problem

Alcohol use disorders are understudied in Europe, despite their prevalence. SyBiL-AA is a multidisciplinary, EU-wide project that is employing a broad range of techniques to find a better way of approaching this issue.

Alcohol use disorders, of which the most serious is alcohol addiction or alcoholism, represent a significant burden in many parts of the world, but nowhere more so than Europe. The EU currently has the highest consumption of pure alcohol per person out of any region across the globe – 11 litres per year – and it is estimated that nearly 20 million Europeans suffer from some form of alcohol use disorder. With studies suggesting that excessive alcohol consumption is more harmful to users than smoking, cocaine or even heroin, something clearly needs to be done.

Yet despite this obvious need for a concerted scientific effort to investigate causes and treatments for alcoholism, Europe is actually lagging behind other parts of the world in this regard. Europe has nothing comparable to the US National Institute on Alcohol Abuse and Alcoholism, or Australia’s National Drug and Alcohol Research Center, and while there are labs dotted around the region that focus on alcohol use disorders, they are not interconnected.

It was in this context that Professor Dr Wolfgang Sommer, a researcher at the Central Institute of Mental Health, Germany, and himself a former unit director at the NIAAA, decided a concerted effort was required to unite European alcoholism research. While the continent may be lacking in viable medical research. By leveraging Europe’s theoretical models to identify brain sites and functional networks in selected patient populations, which can be targeted specifically by therapeutic interventions, the SyBiL-AA project will take an unbiased look at the whole brain. Accumulated new knowledge about the ‘relapse-prone’ network will result in objectively defined disease phenotypes, non-invasive brain network strategies and pharmacological interventions that can provide highly efficient and well tolerated personalised treatments, something that is largely missing presently, says Sommer. Besides this, another goal for the SyBiL-AA researchers is to identify biomarkers that indicate vulnerability to alcoholism early in life, something that would facilitate early detection and reduce harm.

The methods employed by the researchers are diverse, and are carried out on humans where possible, and rats when direct interference with the brain is necessary. MRI can be used in both humans and animals, and is a useful means of mapping the brain. ‘The way activity correlates between different brain regions determines functional connectivity. Having obtained this information graph theory is employed to formally characterise the structure and dynamics of brain networks. Graphs or networks are a set of objects (in our case brain regions) connected through a set of links. There are a large variety of computational methods to characterise these networks. We search for differences between different clinical groups, trying to identify key brain regions and to make predictions about their functionality,’ says Dr Maria Ercsey-Ravasz, a physicist working on the network. In addition, a novel technique, based on the principles of systems medicine, that uses mathematical and network theoretical models to identify brain sites and functional networks in selected patient populations, which can be targeted specifically by therapeutic interventions, explains Professor Sommer. Their approach is highly integrative and interdisciplinary, and it is based on a back-and-forth dialogue between theoretical predictions and experimental validations.

Specifically, the researchers will use magnetic resonance imaging (MRI) of the brain together with neurochemical data from patients and laboratory animals to build a model of the ‘relapse-prone’ state of the brain – learning about the neural characteristics that make people with alcohol use disorders relapse when they attempt to quit. Following this, they will validate their model by going back to in vivo experiments using both human and animal models. Having established the predictive power of their models, they will be able to then test new, non-invasive therapies for alcoholism, as well as new pharmacological candidate compounds.

A BROAD METHODOLOGY

SyBiL-AA aims to provide a novel discovery strategy, based on the principles of systems medicine, that uses mathematical and network theoretical models to identify brain sites and functional networks in selected patient populations, which can be targeted specifically by therapeutic interventions.

Project Insights

FUNDING
European Union’s Horizon 2020 research and innovation programme (project number 668818, SyBiL-AA)

PARTNERS AND PRINCIPAL INVESTIGATORS
Professors Wolfgang Sommer, Peter Kirsch Falk Kiefer and Rainer Spanagel, Central Institute of Mental Health, Heidelberg, Germany (Germany)
• Dr Harm Noori and Professor Martin Walter, Max-Planck-Institute for Biological Cybernetics (Germany)
• Professor Dora Duka, University of Sussex (UK)
• Professor Markus Heilig, University of Linköping (Sweden)
• Professor Abraham Zangen, Ben-Gurion University (Israel)
• Dr Raul Muresan and Maria Ercsey-Ravasz, Romanian Institute for Science and Technology – Dr Andreas Bender, Cambridge University (UK)
• Dr Angelo Bifone, Italian Institute of Technology – Dr Santiago Canals, Spanish National Research Council (CSIC)
• Dr Petri Hytöälä, University of Helsinki (Finland)
• Professor Thomas Hankemeier, Leiden Academic Center for Drug Research (Netherlands) – BrainSway, Israel

CONTACT
Wolfgang Sommer
Project Leader
T: +49 621 1703-6286, -6259
E: wolfgang.sommer@zimmannhe.de
W: wwww.sybi-aa.eu

PROJECT LEADER BIO
Professor Wolfgang Sommer is deputy scientific director of the Institute for Psychopharmacology at the Central Institute of Mental Health (CIMH) in Mannheim, Germany, where he also works as a senior psychiatrist in the Clinics for Addiction Medicine. He is also a professor of psychiatry at the University of Heidelberg, Germany.

Dr Maria Ercsey-Ravasz is a researcher at the Experimental and Theoretical Neuroscience Laboratory in Innsbruck, the Austrian Institute of Science and Technology (RISI) in Cluj-Napoca, Romania, where she also works at the Physics Department of the Babes-Bolyai University. Between 2008 and 2011 she has been a postdoctoral researcher at the Interdisciplinary Center of Network Science and Applications at the University of Notre Dame, USA.