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 (NIAAA), 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 research networks for alcohol use disorders, it has seen considerable investment in systems biology, which has been prioritised as an efficient means by which to accelerate medical research. By leveraging Europe's available research infrastructure in systems neurobiology, Sommer and a team of multidisciplinary researchers have developed a highly collaborative project termed Systems Biology of Alcohol Addiction (SyBil-AA).

THE CHALLENGE OF ALCOHOLISM

Treating alcoholism is difficult. Even identifying it presents immediate challenges, as like most mental health disorders its diagnosis is reliant on psychiatrists making subjective decisions. What is more, many of the behavioural and pharmacological treatments that have been tried either lack sufficient evidence, or have only had very limited success. One issue is that besides all the usual difficulties that accompany addictive behaviours, societal factors may play a role in the uptake of new therapies designed to prevent relapse in alcoholics – which tends to be low. 'This is due to the stigma associated with alcoholism,' says Sommer.

What is required is a totally new approach, and the SyBil-AA team thinks that a systems biology framework is the way to go. '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 that can be targeted specifically by therapeutic interventions,' explains 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

The project is truly ambitious in its scope. Up until this point only a handful of brain regions have been systematically studied with respect to their response to treatments, but 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 feedback 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.

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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 in network science, and one of the principal investigators. Those predictions are then validated in rats by direct intervention into the network. In addition, a novel technique known simply as deep transcranial magnetic stimulation (TMS) is being employed by the clinicians of the team as a non-invasive alternative that can therefore be applied in humans to achieve similar results. The therapeutic potential of deep TMS is being exploited by BrainSway, an industry representative that is partnering with the SyBil-AA project.

BUILDING CONNECTIONS

Although the project is still only in its initial stages, SyBil-AA is already producing meaningful findings. Notably, a proof-of-concept study published last year demonstrated the value of their systems approach by overturning previously held assumptions about the neurochemical drivers of relapse behaviour. While it was thought that low levels of dopamine, a chemical associated with pleasure, in the brain of abstaining alcoholics led to relapse, in fact the researchers found increased levels after a few weeks of abstinence. The lesson here is that abstinence and relapse are not straightforward behaviours with fixed neurochemical and functional alterations. This is why the holistic approach taken by SyBil-AA is so beneficial.

Another key output of the project so far has been a new connectome database of rats (ChemNetDB). 'This is based on the team's extensive neuroanatomical and neurochemical work with these rodents, and also advanced neuroinformatics methods that integrate over 50 years of research into ChemNetDB, making it currently the most comprehensive multi-scale database, and it is openly accessible to anyone in the research community', says Ercsey-Ravasz. This exemplifies what the team wants to achieve with their project – not just strive towards their own personal goals, but give back to the research community and reinvigorate a field that has been severely underdeveloped in Europe.

In the same vein, another exciting aspect of the project is the cohort of enthusiastic young researchers that SyBil-AA has attracted. Over the course of the research, they will develop and mature as scientists, and working as part of an interdisciplinary and collaborative project they will not be confined to a particular topic or technique. 'What we are doing in our project is training a new generation of scientists that can apply systems approaches to many unresolved questions in medicine and biology,' Sommer enthuses. This next generation will be needed to continue the work being pioneered by SyBil-AA, because only then can a better system for alcohol use disorders be created; one that employs early detection strategies, and effective personalised interventions.

Project Insights

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SyBil:AA Systems Biology of Alcohol Addiction

European Commission