Proposals for the Alicia Koplowitz Foundation PhD Fellowships

PROJECT PROPOSAL NUMBER 1

Internet-delivered treatment for anxiety-related disorders in youth with Autism Spectrum Disorder: A randomised controlled trial with health economic evaluation and long-term follow-up

Up to half of young people with Autism Spectrum Disorder (ASD) have comorbid anxiety or obsessive-compulsive disorders, though these disorders are seldom treated with evidence-based approaches. Mounting evidence suggests that these common mental disorders can be successfully managed with cognitive-behaviour therapy (CBT) specifically adapted for persons with ASD. Unfortunately, treating anxiety-related disorders in persons with ASD is resource-intensive, and such treatment is only currently available at a few specialized clinics in Sweden, creating a huge gap between demand and availability of treatment. Internet-delivered CBT (ICBT) was developed as an innovative solution to overcome existing treatment barriers, with demonstrated efficacy and cost-effectiveness in youth with a range of common mental disorders, including anxiety disorders and obsessive-compulsive disorder (OCD). However, these studies systematically excluded participants with ASD. Therefore, little is known about whether ICBT could be a viable alternative to treat common comorbid disorders (i.e., anxiety and OCD) in patients with ASD. Capitalising on the existing infrastructure available within our research network and experience developing eHealth interventions for several psychiatric and functional somatic disorders in young people, aim to evaluate the efficacy and cost-effectiveness of an ICBT protocol for anxiety-related disorders specifically adapted for the needs of persons with high functioning ASD. We will partner with patients, families, and clinicians to further develop this intervention and evaluate its efficacy, durability, and cost-effectiveness in a fully powered randomized controlled trial (N=92 participants) with a long-term follow-up (12 months after treatment). We will also perform a cost-effectiveness evaluation of the intervention from the healthcare and societal perspectives. If successful, the intervention will be implemented in Stockholm's new CAMHS Internet treatment clinic.

PROJECT PROPOSAL NUMBER 2

Identifying targets for prevention in Obsessive-Compulsive Disorder (the OCDTWIN study)

Obsessive-compulsive disorder (OCD) is a common and impairing disorder which strongly affects quality of life and presents a burden to the individual as well as society at large. Despite dedicated research, the causes of OCD remain largely unknown. Gene-searching efforts are well underway but the identification of specific environmental risk factors should be regarded as a scientific priority because some of these risk factors may be amenable to early intervention and prevention strategies. Genetically-informative studies, in particular those employing the discordant monozygotic (MZ) twin design, are ideally suited to study environmental risk factors. In Sweden, we have launched OCDTWIN, an ambitious project to create the world's first cohort of MZ twin pairs where at least one twin has a confirmed diagnosis of OCD. We are building a unique biobank of biological specimens, including blood, saliva, urine, stool, hair, and brain imaging data from MZ twin pairs. Data on other prenatal and early-life environmental exposures (e.g., obstetric complications, childhood infections, childhood stress) will be available through linkage with the Swedish nationwide registers. We will identify environmental risk factors (e.g., epigenetic changes) that are in the causal pathway to OCD through within-pair comparisons of discordant MZ twins, which will allow us to isolate the impact of unique environmental factors, while strictly controlling for genetic and shared environmental influences. The innovative project design, along with the unique data available in the Swedish registers and existing infrastructure, provide an unparalleled opportunity to generate new insights into the potentially modifiable causes of OCD. The study, which is underway (25 MZ twin pairs already recruited), will generate many kinds of data for analysis. Prospective PhD students can focus on various aspects of the study, according to their own personal preference/expertise.

PhD SUPERVISORS

Prof David Mataix-Cols, PhD, leads the Obsessive-Compulsive and Related Disorders Across the Lifespan research group at the Department of Clinical Neuroscience, KI (http://ki.se/en/cns/david-mataix-cols-research-group). He is an internationally leading expert in the field of anxiety, OCD, and related disorders. He also works as a consultant clinical psychologist at the OCD and Related Disorders Clinic for children and adolescents at the Child and Adolescent Psychiatry Research Centre in Region Stockholm. He is the coordinator of the Alicia Koplowitz Foundation advanced training fellowships and the new PhD fellowships hosted at the Karolinska Institutet.

Dr Lorena Fernández de la Cruz, PhD, Senior Researcher, is a clinical researcher specialized in the field of OCD and related disorders. She has clinically trained in Spain and the UK. She currently leads the "Health consequences and lifestyle modification group", which primarily focuses on the long-term medical and socioeconomic consequences of OCD and related disorders and the development of lifestyle interventions.

RESEARCH SETTING AND PRACTICAL ARRANGEMENTS

The PhD student will become part of the Obsessive-Compulsive and Related Disorders Across the Lifespan research group, led by Prof. Mataix-Cols. The group is part of the Department of Clinical Neuroscience (CNS) at Karolinska Institutet (KI) and has strong links with the Child and Adolescent Psychiatry Research Centre within the CAMHS in Region Stockholm. The PhD student will have the necessary desk space as well as access to the Internet and to online library/data searches, the institution's network, and statistical software.

ADDITIONAL TRAINING ACTIVITIES

Doctoral level courses related to the content and methodological skills needed for the development of the epidemiological projects described above will be available at KI (with no cost for the PhD student), such as:

- Basic Course in Medical Statistics
- Clinical Research in Child and Adolescent Psychiatry
- Writing Science and Information Literacy
- To Communicate Science in Different Contexts

- How to Conduct Systematic Reviews and Meta-Analyses
- Medical Research Ethics
- Epidemiology I: Introduction to epidemiology
- Epidemiology II: Design of epidemiological studies
- Biostatistics: Introduction for epidemiologists
- SAS (statistical package for epidemiological studies) for beginners

Additionally, the fellow will be able to attend other educational activities hosted at the Karolinska Institutet and the Child and Adolescent Psychiatry Research Centre, including our monthly Journal Club, trimestral KI OCD Sessions, and several series of periodic lectures at KI (e.g., KI Discovers, the Stockholm Psychiatry Lectures), among many others.

CLINICAL ACTIVITIES

There is the possibility for the PhD student to obtain an honorary clinical contract to participate in clinical sessions at the different clinics within the Child and Adolescent Psychiatry Research Centre (e.g., OCD and related disorders clinic, immunopsychiatry clinic, neurodevelopmental disorders / neuropsychiatry clinic, gender dysphoria clinic, trauma clinic) and other child and adolescent psychiatric clinics within Region Stockholm. However, most sessions will be in Swedish and therefore this option will be linked to the willingness of the PhD student to quickly learn the basics of the Swedish language. The Swedish Government offers free Swedish Courses for Immigrants.

ALICIA KOPLOWITZ FUNDACION

APPLICATION FOR PhD FELLOWSHIP

Applicant and proposed external PhD supervisor: Prof. dr. Jim van Os
Division Neuroscience
Utrecht University Medical Centre
The Netherlands
j.j.vanos-2@umcutrecht.nl

A. Credentials of supervisor and host institute:

Personal statement

I have obtained funding for, and supervised over 60 PhD projects. Over the period 2009-2015, I was coordinator of a €12M EU FP7 IP project on gene-environment interactions in schizophrenia; over the period 2006-2012, I was member of the Psychosis Group of the DSM-5 Task Force. I am Chair of the Division Neuroscience at Utrecht University Medical Centre, which hosts the Brain Center Rudolf Magnus, one of the most stimulating neuroscience research environments in Europe (https://www.umcutrecht.nl/en/Research/Research-programs/Brain-Center-Rudolf-Magnus). The Division Neuroscience employs 1200 people including a very active child and adolescent psychiatric department with an active focus on psychosis, autism and other mental disorders, as well as a child neurology and child neurosurgery department. Utrecht University Medical Center also has a very active general Child Health Research program (http://www.umcutrecht.nl/en/Research/Research-programs/Child-Health-science-for-life).

I am fluent in Spanish and chair of the external supervisory committee of the Spanish CIBERSAM network in psychiatric research. As such, I have many links with all the major research departments throughout Spain.

Positions and Honors

In 2011, I was elected member of the Royal Netherlands Academy of Arts and Sciences (KNAW); I appear on the 2014 & 2015 Thomson-Reuter *Web of Science* lists of the world's 'most influential scientific minds' of our time. In 2016, I was awarded the title of *Fellow* at King's College London.

Other relevant experience and professional memberships

Editorial board positions: European Psychiatry; Acta Psychiatrica Scandinavica; Schizophrenia Research; Psychological Medicine; Journal of Mental Health; Schizophrenia Bulletin; Early Intervention in Psychiatry; Psychosis Journal; Epidemiology and Psychiatric Sciences. Academic Editor, PLoS ONE

Web of Science Hirsch Index: 94; Google Scholar: 125

B. Contribution to Science

Gene-environment interactions

I have been an early and leading researcher in the area of gene-environment interactions, and as a result became PI-coordinator of a €12M EU FP7 IP project on gene-environment interactions in schizophrenia (2009) and co-PI of the €4M Dutch collaborative GROUP project on gene-environment interactions. Some peer-reviewed publications in this area are:

GROUP (2011). Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. *Arch Gen Psychiatry* **68**, 138-47.
van Os, J., Kenis, G. & Rutten, B. P. (2010). The environment and schizophrenia. *Nature* **468**, 203-12.
van Os, J., Rutten, B. P. & Poulton, R. (2008). Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr Bull* **34**, 1066-82.
van Winkel, R. and GROUP (2011). Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. *Archives of General Psychiatry* **68**, 148-57.
van Os, J., Marsman, A., van Dam, D., Simons, C. J. & GROUP Investigators. (2017). Evidence That the Impact of Childhood Trauma on IQ Is Substantial in Controls, Moderate in Siblings, and Absent in Patients With Psychotic Disorder. Schizophr Bull 43, 316-324.
van Os, J., van der Steen, Y., Islam, M. A., Guloksuz, S., Rutten, B. P., Simons, C. J. & GROUP Investigators. (2017). Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience. Psychol Med, 1-17.

Extended phenotypes of mental disorders.

One of the main problems facing psychiatric research is phenotypic definition. We have spearheaded efforts to define novel subthreshold phenotypes of psychosis, mania and depression based on subtle psychometric expressions of liability in the general population cohorts. This work has led to an explosion of research by many groups worldwide and is impacting research using genetic and neuroimaging approaches. Some peer-reviewed publications in this area are:

Dominguez, M. D., Saka, M. C., Lieb, R., Wittchen, H. U. & van Os, J. (2010). Early expression of negative/disorganized symptoms predicting psychotic experiences and subsequent clinical psychosis: a 10-year study. *Am J Psychiatry* 167, 1075-82.

van Os, J. & Reininghaus, U. (2016) Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry*, **15**, 118-124.
Van Os, J., Hanssen, M., Bijl, R. V. & Vollebergh, W. (2001). Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. *Arch Gen Psychiatry* 58, 663-8.
Van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P. & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med* 39, 179-95.
van Os, J. & Guloksuz, S. (2017). A critique of the "ultra-high risk" and "transition" paradigm. World Psychiatry 16, 200-206.
van Os, J. & Reininghaus, U. (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry 15, 118-24.

Momentary assessment technology in psychiatry

We have developed novel phenotypic approaches based on intensive time series experience sampling methodology (ESM) that can be used to construct mental state networks, allowing the study of gene-environment interactions impacting on network connections in the flow of daily life. In addition, we have developed am mHealth platform based on ESM for diagnosis, evaluation of treatment and momentary assessment interventions in mental health. Some peer-reviewed publications in this area are:

Myin-Germeys, I., Krabbendam, L., Jolles, J., Delespaul, P. A. & Van Os, J. (2002). Are cognitive impairments associated with sensitivity to stress in schizophrenia? An experience sampling study. *Am J Psychiatry* 159, 443-9.
Myin-Germeys, I., van Os, J., Schwartz, J. E., Stone, A. A. & Delespaul, P. A. (2001). Emotional reactivity to daily life stress in psychosis. *Arch Gen Psychiatry* 58, 1137-44.
Van Os, J., Delespaul, P., Wigman, J., Myin-Germeys, I. & Wichers, M. (2013). Beyond DSM and ICD: introducing "precision diagnosis" for psychiatry using momentary assessment technology. *World Psychiatry* 12, 113-7.
Van Os, J., Lataster, T., Delespaul, P., Wichers, M. & Myin-Germeys, I. (2014). Evidence that a psychopathology interactome has diagnostic value, predicting clinical needs: an experience sampling study. *PLoS One* 9, e86652.
van Os, J., Verhagen, S., Marsman, A., Peeters, F., Bak, M., Marcelis, M., Drukker, M., Reininghaus, U., Jacobs, N., Lataster, T., Simons, C., PhD, E.-M. I., Lousberg, R., Guloksuz, S., Leue, C., Groot, P. C., Viechtbauer, W. & Delespaul, P. (2017). The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice. Depress Anxiety 34, 481-493.

Complete List of Published Work in PUBMED: http://bit.ly/2CW7oUV

C. Proposed Research Project

The department has access to a unique collection of large datasets that are relevant to the study of psychosis and affective liability in children, adolescents and transition psychiatry populations (age 12-25 years). We propose first authorships in a research project that will analyse data from the datasets summarized in Table 1. The proposed projects are just examples; the department in fact has a wide range of clinical and population-based datasets with many rich research questions that can be analyzed and published. For example, we have just collected a novel twin study (in the context of our EUGEI project) in a mostly adolescent population, with a wide range of experimental and observational (including Experience Sampling Technology) social defeat, aberrant salience, probabilistic reasoning and many other types of data that can be examined in gene-environment interaction paradigms in association with phenotypic expression of liability of psychosis, depression and mania.

Table 1. Datasets and hypotheses.

STUDY TOPIC	SAMPLE	HYPOTHESIS
Childhood auditory verbal hallucinations (AVH) study.	The data pertains to a case-control sample of 694 children with auditory verbal hallucinations (AVH) at age 7-8 (baseline), and follow-ups of this sample at ages 12-13 (n=337) and again at ages 18-19 years (n=293) (Bartels-Velthuis *et al.*, 2010).	We will examine the predictive value of AVH characteristics, measured with the Auditory Vocal Hallucination Rating Scale interview, on 5-year and 11-year outcomes of: (i) AVH persistence, (ii) onset of delusional ideation, (iii) associations with CBCL-measured problem behaviour.
Childhood psychotic experiences (PE) in relation to cognition and the mediating role of trauma	The data pertains to a high risk cohort study of psychiatric disorders in childhood (Salum *et al.*, 2015). The cohort consists of 2512 children, of whom 958 were randomly selected and 1554 were at higher than average genetic risk because of mental disorders in the family. Detailed psychology interviews were conducted on, amongst others, cognition, trauma and psychotic experiences (PE).	We will examine the association between PE and cognitive alterations, and to what degree associations may be mediated by experience of childhood trauma.
Adolescent-onset psychosis: impact on sibling-patient endophenotype correlations	The Dutch GROUP sample is a unique cohort of 1119 patients with psychotic disorder (Korver *et al.*, 2012), of whom 277 (25%) with adolescent onset. Uniquely, the dataset also contains data based on detailed interviews with 1057 siblings of these 1119 patients, allowing for analysis of both cross-trait and within-trait, cross-sib analyses.	We will test the hypothesis that adolescent onset of psychotic disorder in the patient impacts the expression of psychopathological, neurodevelopmental and environmental liability in the sibling, suggesting that adolescent onset mediates illness severity, the expression of which clusters in families.
EUGEI WP4 Adolescent Twin Sample	This is a unique sample that has just become available through the EUGEI project. Adolescent twins in the general population were extensively genotyped as well as characterised phenotypically and in relation to the environmental exposome, including Experience Sampling, with a focus on social defeat.	We will test hypotheses focussing on GxE using both direct and indirect measures of genetic risk, with subthreshold psychopathology as outcome.

Bartels-Velthuis, A.A., Jenner, J.A., van de Willige, G., van Os, J. & Wiersma, D. (2010) Prevalence and correlates of auditory vocal hallucinations in middle childhood. British Journal of Psychiatry, 196, 41-46.

Korver, N., Quee, P.J., Boos, H.B., Simons, C.J., de Haan, L. & investigators, G. (2012) Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. International Journal of Methods in Psychiatric Research, 21, 205-221.

Salum, G.A., Gadelha, A., Pan, P.M., Moriyama, T.S., Graeff-Martins, A.S., Tamanaha, A.C., et al. (2015) High risk cohort study for psychiatric disorders in childhood: rationale, design, methods and preliminary results. Int J Methods Psychiatr Res, 24, 58-73.

D. Training

The Division Neuroscience at Utrecht University Medical Centre has an extensive program of PhD training courses that will be made available for the candidate. The courses include English writing skills, presentation skills, basic statistics, advanced statistics, Experience Sampling Technology, use of Stata statistical programming, analysis of multilevel data, planning and organizing, scientific integrity and other courses.
During the two years, the candidate will receive personal supervision from Prof. Dr. Jim van Os and senior members of the Department of Psychiatry and Child Psychiatry.

The candidate is welcome to conduct clinical sessions in, for example, transition psychiatry or adolescent psychiatry, however knowledge of the Dutch language is required as the proportion of English speaking patients in child and adolescent psychiatry in the Netherlands is limited.

E. Budget (in euro's)

Cost	Year 1	Year 2	*Total*
0.025 FTE J. van Os principal supervisor	7.314	7.378	14.692
0.025 FTE senior co-supervisor (Dr. Schnack)	1.915	1.983	3.898
0.025 FTE data access supervisor (Dr. Guloksuz)	2.711	2.735	5.446
Data collection contribution	15.500	15.500	31.000
Training courses	2.500	2.500	5.000
Conference attendance	750	750	1.500
Travel	3.000	3.000	6.000
Division Neuroscience overhead (33%)	11.117	11.169	22.286
Total	44.807	45.015	89.822