

## Joint European and South African Research Network in Anxiety Disorders (EUSARNAD)

Prof. David Baldwin (EUSARNAD Project Coordinator) and Miss Magda Nowak (ADRN Administrator)

### INTRODUCTION

Anxiety disorders are common, distressing and impairing conditions – but many people remain undiagnosed and the standard of care received is usually sub-optimal. Although advances in genetics, neuroscience, pharmacology and psychology research have all deepened our understanding of anxiety disorders, on an individual basis it remains difficult to predict who will become troubled by symptoms and difficult to make treatment decisions which would result in better clinical outcomes for the patient.

The European and South African Research Network in Anxiety Disorders (EUSARNAD) aims to provide an international collaborative network for sharing clinical databases, refining research methodologies, and developing and evaluating innovative treatments for patients with anxiety disorders. EUSARNAD thereby contributes to initiatives to enhance understanding of the causes of anxiety disorders and to the development and improved delivery of improved treatments. During the three-year programme, individual exchange researchers are affiliated to research active teams in each of the participating institutions. They gain access to the knowledge and expertise at each participating centre and are also able to attend local postgraduate training programmes within the host institutions.

The EUSARNAD project currently includes 13 centres of excellence for research into anxiety disorders and builds on the Anxiety Disorders Research Network (ADRN) itself supported by the European College of Neuropsychopharmacology Network Initiative (ECNP-NI) (Table 1).

EUSARNAD aims to strengthen links and extend current collaborative work with the University of Cape Town. It allows South African early stage researchers to gain first-hand experience of certain research methodologies in European centres, and helps European early stage researchers to develop a greater understanding of the origin of anxiety disorders and problems in their management within an emerging country. As such EUSARNAD enhances the relevance of translational research activity to both developed and developing societies.

EUSARNAD is funded by the European Commission, through the Marie Curie Actions (People) International Research Staff Exchange Scheme awarded in August 2011 (project number PIRSES-GA-2010-269213). Funding provision relates only to the additional costs of participating exchanged researchers being placed at a distance from their usual institution: these additional costs are principally due to flights and accommodation: no funds are provided for salaries or administrative support.

**Table 1. List of participating centres and their research representatives**

Participating centre	Research representative
University of Southampton, United Kingdom	Professor David Baldwin (project co-ordinator)
Bristol University, United Kingdom	Professor Glyn Lewis
University of Hertfordshire, United Kingdom	Professor Naomi Fineberg
Leiden University, The Netherlands	Professor Nicholas van der Wee
Göttingen University, Germany	Prof. Borwin Bandelow
Gothenburg University, Sweden	Professor Elias Eriksson
Uppsala University, Sweden	Professor Mats Fredrikson
Tartu University, Estonia	Professor Andres Metspalu
Milan University, Italy	Professor Bernardo Dell'Ossio
Cantabria University, Spain	Professor Jose-Luis Vazquez Barquero
University of Tel Aviv, Israel	Professor Joseph Zohar
University of Cape Town, South Africa	Professor Dan Stein

EUSARNAD provides the framework for training of early stage researchers in a number of methodologies relevant to research into the causes and treatment of anxiety disorders. Table 2 lists the work packages.

Table 2. EUSARNAD work packages

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|-----|---|
| 1.  | Institution of the project ethics and regulatory committee and steering committee |
| 2.  | Development of a computerised collaborative database                              |
| 3.  | Training in exploring endophenotypes in anxiety disorders                         |
| 4.  | Training in exploring genetic polymorphisms in anxiety disorders                  |
| 5.  | Training in neuroimaging and peripheral studies in anxiety disorders              |
| 6.  | Training in epidemiological studies of outcome in anxiety disorders               |
| 7.  | Building a platform for randomised controlled trials                              |
| 8.  | First EUSARNAD colloquium   |
| 9.  | Second EUSARNAD colloquium  |
| 10. | Training in systematic reviews and meta-analyses in anxiety disorders             |
| 11. | Preparation and submission of EUSARNAD final study report                         |

### ACTIVITIES WITHIN EUSARNAD BETWEEN OCTOBER 2011 and FEBRUARY 2013

The first exchange researcher, Sonja Pasche, a clinical psychologist, joined the University of Southampton in October 2011. The main aim of her visit was to investigate the relationships between anxiety symptoms and substance use disorders through contributing to the Attentional Biases in Alcohol Use Disorders study (ABAUD). In addition Miss Pasche had the opportunity to attend the regional Mood Disorders Service outpatient clinic and to lecture third year medical students. She has also participated in the Society for the Study of Addictions conference in York in November 2011. Her visit has already resulted in one publication (Pasche S, Myers B. Substance misuse trends in South Africa. *Hum Psychopharmacol* 2012; 27: 338–341); two manuscripts relating to the ABAUD study findings have been submitted, and one of these has been accepted for publication in *Journal of Studies on Alcohol and Drugs*.



Sonja Pasche

Miss Pasche said: “My visit to Southampton provided a wonderful opportunity to engage with colleagues from a variety of backgrounds. EUSARNAD is a worthwhile initiative, allowing young researchers and clinicians to explore ideas, enhance their knowledge and build a network of colleagues across the globe.”

Jean-Paul Fouche visited the Leiden University Medical Centre (LUMC) between January–March 2012. He collaborated in the examination of an existing dataset, derived from the long-standing Netherlands Study of Depression and Anxiety (NESDA), focusing on the neuroimaging findings. Mr Fouche assisted with analyses of resting state functional MRI data and played a pioneering role in building a collaborative research consortium for MRI mega-analyses. During his visit to LUMC he was able to highlight potential research opportunities within the CUBIC centre, which is a collaborative unit involving the Universities of Cape Town and Stellenbosch. On returning to South Africa he has undertaken an important mentoring role for subsequent EUSARNAD exchangees.



JP Fouche

His visit resulted in the second EUSARNAD supported publication (Fouche JP et al. Recent advances in the brain imaging of social anxiety disorder. *Hum Psychopharmacol* 2013; 28: 102–105).

Natasha Strydom visited the Estonian Genome Research Centre at the University of Tartu for a period of six months (June–November 2012). She underwent training in mRNA and microRNA expression analysis using several bioinformatic tools in the laboratory led by Professor Metspalu, and gained experience of research in the areas of epigenetics and genome wide association studies. Whilst in Tartu, Miss Strydom started writing a review of peripheral gene expression in anxiety disorders, which is now in an advanced stage of preparation.



Natasha Strydom

Natalie Cuzen was affiliated to the University of Hertfordshire between June and December 2012. She undertook research into impulsivity and compulsivity in patients with obsessive–compulsive disorder and comorbid alcohol dependence, in collaboration with the University of Cambridge. She also had the opportunity to attend the UK National Specialist OCD Service led by Professor Fineberg. In addition Miss Cuzen had the opportunity to attend the Annual Meeting of the British Association of Psychopharmacology (Harrogate, July 2012), and to present research findings at the European College of Neuropsychopharmacology (Vienna, October 2012), the ICOCs meeting (Vienna, October 2012), and the European Psychiatric Association (Nice, April 2013).



Natalie Cuzen

Anne Uhlmann was attached to the Department of Psychiatry and Psychotherapy at the University of Göttingen between June–July 2012. She collaborated in an investigation of morphological differences in the brains of patients (3-T MRI images) with alcohol use disorders, with or without depressive or anxiety disorder comorbidity. She is undertaking a review of anxiety symptoms and anxiety disorders in habitual methamphetamine users.



Anne Uhlmann

Miss Uhlmann says: "I believe that the inspiration that all exchangees took from the EUSARNAD programme will surely reflect in our respective careers going forward. It has been a truly rewarding experience to meet and establish relationships with new mentors and fellow researchers."

Coenraad (Coenie) Hattingh was attached to the Leiden University Medical Centre in December 2012. He joined a research tea, investigating mood, anxiety and post-traumatic disorders in children and adolescents; and undertook training in analytic methods for studies of cortical thickness in adolescents. Like JP Fouché, Coenie established close working relationships with two PhD students (Nienke Pannekoek and Steven van der Werff), paving the way for the reciprocal component of the exchange in early 2013.



Coenie Hattingh

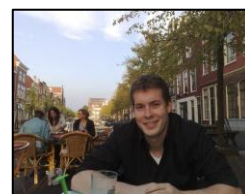
All EUSARNAD exchangees who had undertaken an attachment prior to December 2012 participated in the EUSARNAD Colloquium timed to coincide with the International Anxiety Disorders Symposium (IADS), held outside Cape Town in February 2013. All of the exchangees submitted abstracts for poster presentation; and all were accepted for presentation and publication in a supplement to the *African Journal of Psychiatry*. At the time of the Colloquium, five other EUSARNAD exchangees had rotated from European centres to Cape Town: all attended the IADS and participated in the Colloquium. A sixth exchange (Sarah Heany) had rotated from Cape Town to Leiden. The following paragraphs provide a brief account of the activities which these exchangees were undertaking at the time of the Colloquium.

Sarah Heany from Cape Town was attached to the Leiden University Medical Centre between January and March 2013. The aims of the attachment were to acquire skills and experience in (functional) neuroimaging, including choice of study design, development and piloting of social paradigms, acquisition of functional MRI scans and an introduction to simple first and second level analyses. During her stay in Leiden Sarah acquired several of these basic skills, and undertook training in the two most important MRI analysis software packages, namely FSL and SPM. She also visited the MRI laboratory of Professor van Honk at Utrecht University, to gain experience with fMRI paradigms that she will use in her own PhD project in Cape Town. She also started an editorial on the influence of neuropeptides and hormones on social interaction.

Justine (Nienke) Pannekoek and Steven van der Werff were the first researchers to visit UCT from Leiden, being attached to UCT from mid-January 2013 for a period of 4 weeks. Both Nienke and Steven had previous experience of the analysis of MRI data and so were able to continue the collaboration established through the attachment of previous exchangees (JP Fouche, Coenie Hattingh) to Leiden. They also helped initiate an international consortium to collate and analyse MRI studies of individuals with social anxiety disorder: the first step was to quality-check existing scans in the consortium, with an inter-rater reliability study. They undertook some additional training activities, including a neuroanatomy seminar with dissection of a human brain, supervised by Coenie Hattingh, and attended local lectures and symposia which increased their knowledge of challenges faced by mental health services in South Africa. Both started writing articles for the EUSARNAD series in *Human Psychopharmacology*, and Nienke started a chapter on 'illness anxiety disorder' in collaboration with Professor Stein. Both presented EUSARNAD work at the International Anxiety Disorders Symposium, the abstracts being published in the *African Journal of Psychiatry*.



Nienke Pannekoek



Steven van der Werff

Nienke and Steven write: "We completed our first brain dissection under guidance of Coenie. He taught us a lot about the anatomy of the brain and it was really interesting to finally see the organ we have been so busy studying these last couple of years. We can highly recommend this experience to all neuroresearchers as it really gives a better perspective and understanding on how the brain is structured".

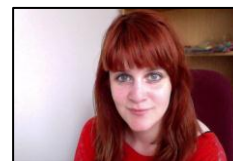
Andy Crawford from the University of Bristol was attached to UCT between January and February 2013. He was engaged in an investigation involving haplotype analysis comparing individuals with alcohol dependence (with and without anxiety) with healthy controls. He made contact with Shareefa Dalvie, a researcher with similar interests, who hopes to be exchanged to Bristol later in 2013; and gained experience of MRI scanning through being a "healthy control" in a study investigating drug abuse. He gave a presentation titled "EUSARNAD, ALSPAC and antidepressant-induced adverse effects", which described the dataset available in Bristol, and the potential for collaboration. He took the opportunity of being in Cape Town to train with a local water polo team and played a match for them (which they won)! After his visit he said: "EUSARNAD allowed me to meet researchers from different disciplines all interested in gaining a greater understanding of anxiety disorders. Investigating the unique genetic profiles found in South African populations has the potential to discover valuable insight into the genetics of anxiety disorders."



Andy Crawford

Carlotta (Lotte) Palazzo a psychiatrist from the University of Milan was attached to UCT between January and March 2013. She undertook a systematic review of health literacy about pharmacological treatment in

anxiety disorders, and a systematic review of the response of psychological and somatic symptoms of anxiety to pharmacological treatment in patients with generalized anxiety disorder. She presented the findings of her international collaborative study (involving three EUSARNAD partners: Milan, Calabria, Southampton) of a questionnaire for eliciting data on the duration of untreated illness and the interval before treatment in patients with mood or anxiety disorders at the IADS meeting, and was awarded the prize for the best poster. The review of health literacy has been prepared for submission as part of the EUSARNAD series in *Human Psychopharmacology*.



Carlotta Plazzo

Ben Ainsworth, an experimental psychologist from Southampton, was attached to the CUBIC centre in Stellenbosch, and underwent training in a number of neuroimaging methods and analyses, in particular Freesurfer, under the supervision of JP Fouché. He developed the EUSARNAD 'blog' and became responsible for updating it with reports on the activities of EUSARNAD exchangees. He contributed to the inter-rater reliability study of neuroimaging findings in social anxiety disorder, and undertook a systematic review of the use of the anti-saccade task in studies of anxiety in healthy volunteers and patients with anxiety disorders: the latter has been submitted to and accepted for publication in *Human Psychopharmacology*.



Ben Ainsworth

The Colloquium at the IADS was chaired by Professor Christer Allgulander (Karolinska Institutet, Stockholm) and was judged to be a great success by all the attending exchangees and the centre leads (Professors Baldwin, Bandlelow, Fineberg and Stein).



The following table summarises previous and current exchanges within the EUSARNAD scheme.

<b>EUSARNAD attachments, outputs and awards (as of April 2013)</b>					
<b>Exchange researcher</b>	<b>Travelling from</b>	<b>Travelling to</b>	<b>Dates</b>	<b>Description of research activity</b>	<b>Presentations and publications</b>
Sonja Pasche	UCT	Southampton	October 2011 to January 2012	Training in methods for investigating attentional biases in alcohol use disorders (ABAUD study).	<ol style="list-style-type: none"> <li>1. Pasche S, Myers B. Substance misuse trends in South Africa. <i>Hum Psychopharmacol</i> 2012; 27: 338–341.</li> <li>2. Pasche SC et al. Components of craving and the relation to the severity of alcohol problems. Poster presentation at International Anxiety Disorders Symposium (IADS), Cape Town, February 15–17, 2013.</li> <li>3. Pasche SC et al. 'Craving': Exploring the components of the Desires for Alcohol Questionnaire (DAQ) and the relation to the severity of alcohol problems. <i>Journal of Studies on Alcohol and Drugs</i>. Accepted for publication.</li> </ol>
JP Fouche	UCT	Leiden	January to March 2012	Further examination of existing dataset, derived from the NESDA study, with a focus on neuro-imaging findings.	<ol style="list-style-type: none"> <li>1. Fouche JP, van der Wee NJA, Roelofs K, Stein DJ. Recent advances in the brain imaging of social anxiety disorder. <i>Hum Psychopharmacol</i> 2013; 28: 102–105</li> <li>2. Fouche JP, du Plessis S, Hattingh C et al. Examining cortical thickness in subjects with obsessive-compulsive disorder: A Freesurfer analysis of a multi-site cohort. Poster presentation at IADS 2013.</li> </ol>
Natasha Strydom	UCT	Tartu	June to Sep 2012	Training in methods of analysis of peripheral gene expression.	<ol style="list-style-type: none"> <li>1. Strydom N. Estonia and EUSARNAD. Poster presentation at IADS 2013.</li> </ol>
Natalie Cuzen	UCT	Welwyn Garden City	June to Dec 2012	Training in research into endophenotypes through an investigation of alcohol use disorders in OCD.	<ol style="list-style-type: none"> <li>1. Lochner C, Fineberg NA, Cuzen NL, et al. A cross-sectional study of Axis I and obsessive-compulsive spectrum disorder comorbidity patterns in primary OCD. Poster presentation at International College of Obsessive Compulsive Spectrum Disorders (ICOCs), Vienna, 18<sup>th</sup> October 2012.</li> <li>2. Cuzen NL et al. Substance use in obsessive-compulsive disorder: what does it mean? Poster presentation at ICOCs 2012.</li> <li>3. Cuzen NL et al. Does substance use compound impulsivity in obsessive-compulsive disorder? Poster presentation at IADS 2013.</li> <li>4. Cuzen NL et al. Brain abnormalities associated with stimulant dependence – does gender matter? Oral presentation at EPA 2013, Nice.</li> </ol>
Anne Uhlmann	UCT	Goettingen	June–July 2012	An investigation of morphological differences between patients with alcohol use disorders, with or without anxiety disorder comorbidity.	<ol style="list-style-type: none"> <li>1. Uhlmann A, Bandelow B, Stein DJ et al. Structural brain differences in alcohol dependent subjects with and without comorbid affective pathology – a retrospective MRI study. Poster presentation at IADS 2013.</li> </ol>
Coenie Hattingh	UCT	Leiden	Dec 2012	Training in analytic methods for studies of cortical thickness in adolescents.	<ol style="list-style-type: none"> <li>1. Fouche JP, du Plessis S, Hattingh C et al. Examining cortical thickness in subjects with obsessive-compulsive disorder: A Freesurfer analysis of a multi-site cohort. Poster presentation at IADS 2013.</li> </ol>
Carlotta Palazzo	Milan	UCT	January – March 2013	Investigation of barriers to drug treatment in anxiety disorders; meta-analysis of reduction in psychic and somatic anxiety symptoms in GAD.	<ol style="list-style-type: none"> <li>1. Palazzo MC, Dell'Osso B, Arici C et al. Developing a new tool for assessment of onset symptoms and latency to treatment in psychiatric disorders: the POLT-Q. Poster presentation at IADS 2013</li> <li>2. Awarded prize for best post presentation at IADS.</li> </ol>
Sarah Heany	UCT	Leiden	January–March 2013	Training in functional neuroimaging; review of the influence of neuropeptides and hormones on social interaction.	Attached to Leiden in February 2013 and so unable to participate in Colloquium.



# Report from First EUSARNAD Colloquium, February 2013

Andrew Crawford	Bristol	UCT	January–February 2013	Investigation of genetic correlates of anxiety symptoms in substance use disorders.	<ol style="list-style-type: none"> <li>1. Crawford A et al. Severity of anxiety and response to citalopram or reboxetine: GENPOD randomised controlled trial. . Poster presentation at IADS 2013.</li> <li>2. Crawford A et al. Are baseline physical symptoms characteristic of severe depression or a poor prognostic factor? A secondary analysis of the GENPOD trial. Poster presentation at IADS 2013.</li> </ol>
Steven van der Werff	Leiden	UCT	January–February 2013	Continue the collaboration established through the attachment of previous exchangees Leiden; initiation of an international consortium to collate and analyse MRI studies of individuals with social anxiety disorder; quality-checking existing scans in the consortium, through an inter-rater reliability study.	<ol style="list-style-type: none"> <li>1. van der Werff S et al. Resting-State functional connectivity in adults with childhood emotional maltreatment. Poster presentation at IADS 2013.</li> <li>2. van der Werff, S.J.A. et al. Neuroimaging of resilience to stress: current state of affairs. Hum. Psychopharmacology. Submitted.</li> </ol>
Justine (Nienke) Pannekoek	Leiden	UCT	January–February 2013	Continue the collaboration established through the attachment of previous exchangees Leiden; initiation of an international consortium to collate and analyse MRI studies of individuals with social anxiety disorder; quality-checking existing scans in the consortium, through an inter-rater reliability study.	<ol style="list-style-type: none"> <li>1. Pannekoek JN et al. Aberrant resting-state functional connectivity in limbic and salience networks in treatment-naïve depressed adolescents. Poster presentation at IADS 2013.</li> </ol>
Ben Ainsworth	Soton	UCT	February – March 2013	Training in methods for neuroimaging, at Brain-Behaviour Institute, Stellenbosch	<ol style="list-style-type: none"> <li>1. The EUSARNAD 'blog'.</li> <li>2. Ainsworth B, Morris L, O'Halloran K et al. Using 7.5% CO2 challenge to evaluate novel psychological treatments for anxiety. Poster presentation at IADS, Cape Town, February 15–17, 2013.</li> <li>3. Ainsworth B, Garner MJ. Attention control in mood and anxiety disorders: evidence from the anti-saccade task. Human Psychopharmacology. In press.</li> </ol>