Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 41
March 2009

RMI symposium November 2008

This year the Rudolf Magnus symposium and evening took place the 26th of November. As each year the symposium highlighted exciting research within the institute with four excellent presentations. The program of the symposium was completed by a keynote lecture of Peter McGuffin, on genes behaviour and mental illness.

Peter McGuffin

The symposium was opened by Marten Smidt of the Dept. Neuroscience and Pharmacology; section neurodevelopment with a lecture on dopamine neurons and development.

Selective neuronal loss in the substantia nigra (SNc), as described for Parkinson's disease (PD) in humans and for Pitx3 deficiency in mice, highlights the existence of neuronal subpopulations. As yet unknown subset-specific gene cascades might underlie the observed differences in neuronal vulnerability. We identified a developmental cascade in mice in which Ahd2 (Aldh1a1) is under the transcriptional control of Pitx3. Interestingly, Ahd2 distribution is restricted to a subpopulation of mesodiencephalic dopaminergic (mdDA) neurons affected by Pitx3 deficiency. Ahd2 is involved in the synthesis of retinoic acid (RA), which has a crucial role in neuronal patterning, differentiation and survival in the brain. Most intriguingly, restoring RA signaling in Pitx3 deficient embryonic mdDA neurons counteracts the developmental defects. The initial rescue by RA treatment during the critical phase was preserved until later in development, and our data suggest that RA is required for the establishment of proper mdDA neuronal identity. Here, we propose a novel mechanism in which RA is involved in mdDA neuronal development and maintenance, providing new insights into subset-specific vulnerability in PD.

Eline Lindeman of the Dept. Rehabilitation and Sportmedicine; section neuromuscular diseases continued with a lecture on the latest research development in the area of rehabilitation.

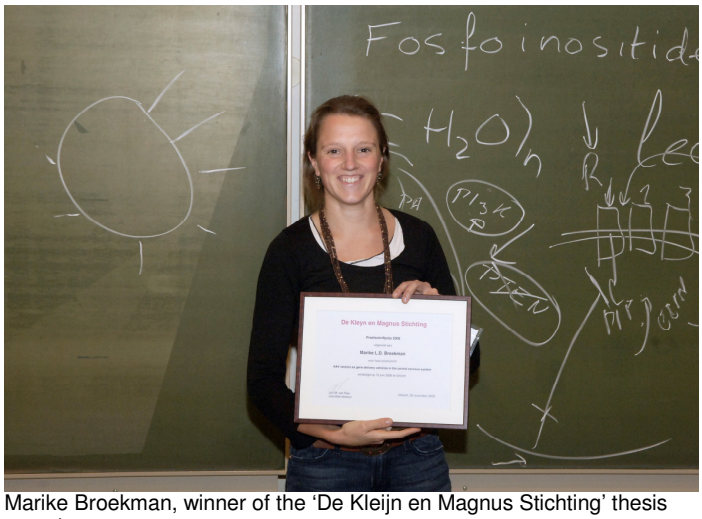
Main claims of the literature are that functional recovery of the paretic upper limb is mainly defined within the first month post stroke and that rehabilitation services should preferably be applied intensively and in a task-oriented way within this particular time window. Explaining PLastICITy after stroke (acronym EXPLICIT-stroke) aims to explore the underlying mechanisms of post stroke upper limb recovery. Two randomized single blinded trials form the core of the programme, investigating the effects of early modified Constraint-Induced Movement Therapy (modified CIMT) and EMG-triggered Neuro-Muscular Stimulation (EMG-NMS) in patients with respectively a favourable or poor probability for recovery of dexterity. 180 participants suffering from an acute, first-ever ischemic stroke will be recruited. Functional prognosis at the end of the first week post stroke is used to stratify patient into a poor prognosis group for upper limb recovery (N = 120, A2 project) and a group with a favourable prognosis (N = 60, A1 project). Both groups will be randomized to an experimental arm receiving respectively modified CIMT (favourable prognosis) or EMG-NMS (poor prognosis) for 3 weeks or to a control arm receiving usual care. Primary outcome variable will be the Action Research Arm Test (ARAT), assessed at 1,2,3,4,5, 8, 12 and 26 weeks post stroke. To study the impact of modified CIMT or EMG-NMS on stroke recovery mechanisms i.e. neuroplasticity, compensatory movements and upper limb neuromechanics, 60 patients randomly selected from projects A1 and A2 will undergo TMS, kinematical and haptic robotic measurements within a repeated measurement design. Additionally, 30 patients from the A1 project will undergo fMRI at baseline, 5 and 26 weeks post stroke. CONCLUSION: EXPLICIT stroke is a 5 year translational research programme which main aim is to investigate the effects of early applied intensive intervention for regaining dexterity and to explore the underlying mechanisms that are involved in regaining upper limb function after stroke. EXPLICIT-stroke will provide an answer to the key question whether therapy induced improvements are due to either a reduction of basic motor impairment by neural repair i.e. restitution of function and/or the use of behavioural compensation strategies i.e. substitution of function.

After the lecture of Eline Lindeman the symposium switched to the world of the neurobiology of auditory verbal hallucinations by Iris Sommer of the Dept. Psychiatry; section psychopathology of developmental disorders.

The pathophysiology of Auditory Verbal Hallucinations (AVH) is largely unknown. Several functional imaging studies have measured cerebral activation during AVH, but sample sizes were relatively small (1-8 subjects) and findings inconsistent. In a recent study of our group, erebral activation was measured using fMRI in 24 psychotic patients. Group analysis for AVH revealed activation in the right homologue of Broca's area, bilateral insula, bilateral supramarginal gyri and right superior temporal gyrus. Group analysis for word generation in these patients yielded activation in Broca's and Wernicke's area and to a lesser degree their right-sided homologues, bilateral insula and anterior cingulate gyri. The main difference between cerebral activity during AVH and activity during normal inner speech appears to be the lateralization. It remains, however, unclear where AVH originate in the brain. In order to reveal the origin of AVH, we identified brain regions showing significant signal changes preceding AVH in fifteen psychotic patients and fifteen control subjects.Prominent deactivation preceding AVH was observed in the left parahippocampal gyrus. In addition, significant deactivation was found in the left superior temporal, right inferior frontal and left middle frontal gyri as well as in the right insula and left cerebellum. No significant signal changes were revealed in the control subjects. It was therefore concluded that AVH in psychotic patients are consistently preceded by prominent deactivation of the parahippocampal gyrus. This could imply that auditory verbal hallucinations are triggered by memory retrieval.

Kees Braun, Dept Neurology and Neurosurgery; section brain function and plasticity, inspired the audience with a lecture on cerebral plasticity in focal childhood epilepsy.

Cerebral plasticity may be important at three different time points throughout the life of a child with epilepsy. First, the *epileptogenic lesion* or event, that occurs during gestation or early in life, will cause structural and functional changes of the brain. Second, the brain will functionally (and possibly also structurally) adapt, once *epileptic seizures* have started and antiepileptic drugs are described. Last, in those who suffer from intractable epilepsy, requiring *epilepsy surgery*, functional recovery depends on the ability of the brain to adapt and compensate for the resection or disconnection of potentially eloquent brain areas. The potential of the developing brain to compensate and reorganize after epilepsy surgery is more pronounced than in adulthood. Even after complete hemispherectomy, behavioral, motor, and cognitive recovery in young children is remarkable. Little is known, however, about the optimal time frame to perform epilepsy surgery in order to guarantee maximal functional recovery. Furthermore, the effects of the frequent and often generalizing seizures on the "healthy" brain are largely unknown. Important decisions in surgical practice would benefit from an increased understanding of age-related plasticity mechanisms of the developing brain in children who face epilepsy surgery.
We hypothesize that the structural and functional integrity of the remaining brain is largely responsible for postoperative functional recovery. In theory, however, several factors may compromise the integrity of the remaining brain, and thereby its ability to compensate for the surgical removal or disconnection of epileptogenic regions. First, diffusion tensor MRI (DTI) has recently demonstrated widespread and remote microstructural abnormalities in predominantly white matter of patients with focal epilepsies. Second, functional reorganization of the remaining hemisphere may lead to a decrease of function of the unaffected body half, since ipsilateral (motor) control from the healthy hemisphere requires recruitment of cortical areas that were originally designated for contralateral innervation. Functional consequences of "crowding" are unknown. Third, the long-term continuation of antiepileptic drugs (AED) after epilepsy surgery may negatively influence the ability of the child's remaining brain to recover, thereby compromising cognitive function, learning, and behavior. In a recently granted research project, we will address these issues in a combined clinical and animal approach. Focal cortical epilepsy will be induced in rats of different ages, followed by hemispherectomy after different time-intervals. Advanced structural and functional high-field *in vivo* MR techniques will be applied longitudinally, to study the integrity and connectivity of the "healthy" hemisphere, in relation to the duration of epilepsy and age at surgery. DTI and fMRI will be used in children with focal epilepsies and after hemispherectomy, to study structural and functional changes in the healthy brain in relation to functional postsurgical recovery. Finally, the safety and possible benefits of early AED withdrawal after childhood epilepsy surgery will be studied in a prospective randomized trial. These studies will improve the selection of surgical candidates, the timing of surgery, and the prediction of functional outcome.



Marike Broekman, winner of the 'De Kleijn en Magnus Stichting' thesis award

The final fascinating lecture of the symposium was given by Peter McGuffin, Institute of Psychiatry London, on genes behaviour and mental illness.

Professor Peter McGuffin is a psychiatrist and is nowadays the Dean and Head of School of the Institute of Psychiatry at King's College in London. His group carried out one of the first genetic marker association studies on schizophrenia. In the keynote lecture during the Rudolf Magnus Symposium, Dr. McGuffin addressed the current status and the future challenges of psychiatric genetics. With the publication of the human genome sequence (in 2001) a new beginning was introduced for biomedical sciences, including psychiatry. He explained that twin and

family studies had already indicated the involvement of both “nature” and “nurture” on behaviour, but that the post-genomic era has opened new ways to study genetic mechanisms underlying psychiatric disorders, such as schizophrenia and bipolar disorders. Dr. McGuffin showed that overlap exists between phenotypic components across these disorders, suggesting that mechanisms relevant to the development of schizophrenia may be involved in bipolar disorders as well. Indeed, genetic studies have now shown associations between certain genes (such as DISC1 and Neuregelin 1) and both schizophrenia and bipolar disorders, confirming this notion. In the past year, genome wide association studies have been performed using large control and case human populations, such as in the Welcome Trust Case Control Consortium (WTCCC) with >15,000 subjects involved. By using these large data sets, novel genes for bipolar disorder, but also for diabetes and obesity, have recently been identified. A next step to take is to gain insights about the function of these genes in the neurobiology of behaviour. This will require functional studies and clues about evolution, as well as understanding of the mechanisms for gene by environment interactions leading to the development of psychiatric disorders. These new insights as well as a more refined diagnosis will become highly relevant for risk prediction and treatment, as pharmacological treatment may or may not work as a function of someone’s genetic variations. With these future perspectives Dr. McGuffin ended his lecture and postulated the question whether this is the end of psychiatry or a new beginning? Obviously, he considers this moment as one of a new beginning with the opportunities of genomic technologies ahead of us.

At the end of the symposium the winners of the Rudolf Magnus Research award and the ‘De Kleijn en Magnus Stichting’ thesis award were announced.

Hylke Blauw and Jan Veldink, winner of the Rudolf Magnus Research award

This year the Rudolf Magnus Research award was presented to the two first authors of a paper published in Lancet Neurology* on genetic riskfactors for ALS. Hylke Blauw and Jan Veldink of the Dept. Neurology and Neurosurgery; section neuromuscular disorders, describe in the paper a genome-wide screen on copy-number variations present in ALS patients and controls. The aim of their research is to determine whether this genetic variation plays a role in the development and progression of ALS.

Marike Broekman had the honor to receive the first ‘De Kleijn en Magnus Stichting’ thesis award for her thesis on the possibilities of gene therapy for brain disease. She wrote her thesis at the Dept. of Neuroscience and Pharmacology and defended in June 2006. Now she works at the Dept. Neurology and Neurosurgery.

*Blauw *et al*., Copy-number variation in sporadic amyotrophic lateral sclerosis: a genome-wide screen. *Lancet Neuroloy* (2008); 7:319-326

PhD theses

Many of our PhD students have defended their thesis in the last couple of months. We want to congratulate all of them with their doctorates.

2008-25
September 4, 2008

K. van Gassen

Molecular characterisation of febrile seizures and temporal lobe epilepsy

J.P.H. Burbach, D. Lindhout, P.N.E. de Graan
Supervisors
Dept. Neuroscience and Pharmacology
Section neurodevelopment

2008-27
September 25, 2008

N. van Orshoven

Autonomic nervous system mediated effects of food intake. Interaction between gastrointestinal and cardiovascular systems

JA.C. van Huffelen, L.M.A. Akkermans, P.L.Oey
Supervisors
Dept. Neurology and Neurosurgery
Section neuromuscular diseases

2008-28
September 30, 2008

P. Halkes

Esprit, European/Australian stroke prevention in reversible ischemia trial and related studies

A. Algra, L.J. Kappelle
supervisors
Dept. Neurology and Neurosurgery
Section cerebrovascular disorders

2008-29
October 30, 2008

M. Raaijmakers

Aggressive behaviour in preschool children. Neuropsychological correlates, costs of service use, and preventive efforts

W.C.H.J. Matthys, H. van Engeland
supervisors
Dept. Child and Adolescent Psychiatry
Section psychopathology of developmental disorders

 editor Mariken de Krom *print* Zuidam&Uithof ISSN 1574-3071

2008-30
November 6, 2008

I. van Kooten

Autism counts stereological studies on human post-mortem brains and a mouse model for autism

H. van Engeland, H.W.M. Steinbusch, C. Schmitz
supervisors
Dept. Child and Adolescent Psychiatry
Section brain changes in developmental disorders

2008-31
November 6, 2008

B. Vastenhouw

Simulation, construction and application of focused pinhole small animal SPECT

M.A. Viergever, F.J.Beekman
Supervisors
Dept. Neuroscience and Pharmacology
Section behavioural phenotyping and genomics

2008-32
November 11, 2008

D. Baas

Suspect the unsuspected Social brain function in schizophrenia and paranoia

R.S. Kahn, A. Aleman, E.H.F. de Haan
Supervisors
Dept. Psychiatry
Section brain changes in developmental disorders

2008-35
November 20, 2008

J. Peper

The early puberal brain: Work in progress. A study on genetic and hormonal influences

H.E. Hulshoff Pol, R.S. Kahn, D.I. Boomsma, R.M. Brouwer
Supervisors
Dept. Psychiatry
Section brain changes in developmental disorders

On the 20th of November, Jiska Peper defended her PhD-thesis on the relative importance of genetic and environmental factors and on pubertal hormones in relation to cerebral gray and white matter at the onset of puberty. Using structural MRI, Peper investigated a large group of 9-year-old twin pairs (N=107 pairs) and their older siblings (N=85) between 10 to 15 years of age.
Results showed that at 9 years of age, individual differences in total brain volume are largely explained by genetic variance (i.e. heritable). However, when zooming in on regional brain areas, it was found that individual differences in gray matter of the frontal lobe are mostly explained by environmental factors, whereas white matter of occipital and temporal areas is highly heritable. Moreover, Peper found that in a very early stage of puberty, luteinizing hormone (LH) is related to increased cerebral white matter in both boys and girls. A common genetic origin could explain the association between LH and white matter. In a more advanced pubertal stage, estradiol levels in girls were predictive of gray matter decreases in frontal and parietal brain areas and increases in temporal and occipital areas. It was concluded that in this important phase of life, different pubertal hormones might be associated with distinct neuroanatomical properties.

2008-36
November 28, 2008

M. Özgen

Morphological features in children with autism

H. van Engeland, F.A. Beemer, R.C.M. Hennekam
Supervisors
Dept. Child and Adolescent Psychiatry
Section genetic basis developmental disorders

2009-1
January 13, 2009

L. Lemmens

Strategies to improve preoperative care

K.G.M. Moons, H.E.M. Kerkkamp
Supervisors
Dept. Anaesthesiology
Section cerebrovascular disorders

2009-2
February 4, 2009

M. Breuer

Depression's next top model: pharmacology of olfactory bulbectomy-induced behaviours

B. Olivier, L. Groenink, R.S. Oosting
Supervisors
Dept. Psychopharmacology
Section behavioural phenotyping and genomics

The aim of the thesis was to provide a better overview of the olfactory bulbectomy model, with regards to its validity as a model for depression, as well as to give further insight to the possible working mechanisms of known and new antidepressants. The thesis also aimed to explore the effects of long- and short-term antidepressant treatment, and how treatment duration and the dose of drug used may lead to different effects after cessation of treatment. Treatment with the tri-cyclic antidepressant imipramine resulted in a fast onset of action, as bulbectomized animals receiving imipramine for three days showed normalized behaviors in the open field. However, the fact remains that most antidepressant treatments are not therapeutically effective until 2-3 weeks of treatment, and further research is necessary not only to discover the mechanism behind this delayed effect, but also how to overcome it. We have also seen that chronic treatment, whether with SSRIs or TCAs, leads to a sustainable effect in the open field paradigm, in that the treated OBX animals remain "normalized" until 6-10 weeks after cessation of treatment. This suggests that antidepressant treatment may perhaps result in semi-permanent changes in brain

plasticity. The results of all these experiments show that the olfactory bulbectomized rat is suitable for the determination of the behavioral effects of new and known antidepressants, but also for examining the onset of action and long- and short-term effects of new and known antidepressant administration. This depression model is useful testing putative new treatments, examining the onset of action, and behavioral effects after cessation of long- and short-term treatment. Since this is one of the few animal models that not only mimics changes in brain neurotransmitters, similar to depressed patients, but also only responds to chronic treatment, it can be said that olfactory bulbectomy is indeed "Depression's Next Top Model".

2009-4
February 26, 2009

R. Mandl

Tract-based analysis in schizophrenia: measuring structure and function along white matter tracts

H.E. Hulshoff Pol
Supervisor
Dept. Psychiatry
Section brain changes in developmental disorders

In the first part of his thesis two properties of fiber bundles connecting frontal and fronto-temporal brain regions were compared between schizophrenia patients and healthy participants. Both microstructural organization and the concentration of macromolecules (including myelin) in the fiber tracts was measured using the fractional anisotropy (FA) measure and magnetic transfer ratio (MTR) imaging, respectively. Using tract-based analysis it was possible to detect very subtle group differences in FA and MTR values that occur along complete fiber tracts. The main finding was an increase in mean MTR for patients in the right uncinate fasciculus. If this increase in mean MTR relates to an increase in myelin then these results suggest that the right uncinate fasciculus plays a compensatory role in schizophrenia. A second finding was a significant age-related decrease in mean FA in the left uncinate fasciculus for patients which was not found in healthy participants suggesting aberrant connectivity between the left frontal cortex and left temporal lobe in schizophrenia.
Although DTI (in combination with fiber tracking) allows the study of *anatomical* aspects of white matter fiber bundles, until now it was not possible the measure the *functioning* of these "information highways of the brain" (techniques such as fMRI, PET, SPECT and MEG only provide functional information of the gray matter of the brain). We developed a new MRI method - which was dubbed functional DTI (fDTI) – with which it is possible to measure activation of these white matter fibers *in vivo*. The results of two studies presented in the second part of this thesis show activation of the sensory thalamocortical tracts and optic radiations during tactile and visual stimulation, respectively. This new fDTI technique is now being optimized so that it can be used to study the functioning of the connecting white matter fiber bundles within a clinically feasible time period. The application of fDTI as a new imaging method is of interest to study the role of the connecting tracts in health and disease.

news and other things

Researchers of the Institute have been successful in obtaining several research grants.

Marten Smidt of the Dept. Neuroscience and Pharmacology obtained two large grants, one personal grant from NWO, a VICI entitled: Molecular programming of mesodiencephalic dopaminergic neuronal subsets. And a collaboration project within the theme Health of the FP7 programme "mdDANEURODEV -Molecular coding and subset specification of dopamine neurons generating the meso-limbic and nigro-striatal system."

Jeroen Pasterkamp of the Dept. Neuroscience and Pharmacology also obtained a TOP-grant entitled "The role of axon guidance molecules in synaptic functions"
René Kahn of the Dept. Psychiatry received a TOP-grant from NWO in collaboration with the UMC Groningen for the proposal "Determinants of the development of bipolar disorder: two follow-up studies."

Eske Derks of the Dept. of Psychiatry was granted a personal grant from NWO, a VENI, with the title "Schizophrenia, what is it and what causes it?"

Bert van der Zwaag of the Dept. Neuroscience and Pharmacology and **Wouter Staal** of the Dept. Child and Adolescent Psychiatry both received a fellowship from the Netherlands Brain Foundation. Staal for the project "Risk genes for autism in relation to structural brain abnormalities. An integration of neuroimaging and genetics" Van der Zwaag for the project "Neurogenomics of autism: Functional consequences of mutations in contactines and contactine-associated proteins for the development of the cerebral cortex."

Kees Braun of the Dept. Neurology and Neurosurgery has been awarded with a personal grant by the National Epilepsy Fund of The Netherlands for his research project entitled; Cerebral plasticity after childhood epilepsy surgery; integrity of the remaining hemisphere determines functional outcome.

Bas Neggers of the Dept. Psychiatry and **Gerry Jager** of the Dept. Neurology and Neurosurgery both received a NWO joint forces grant. Neggers for the project; Response selection and decision making in natural environments: from neuron to behaviour and Jager for the project; The social brain at work; an integrated pharmaco-neuroimaging approach.

Sarah Durston of the Dept. Child and Adolescent Psychiatry receives Brain Foundation award.

October 2008 the Brain Foundation award for research 2008 was presented to Durston. The award is presented every two years and is meant as stimulation for Young researchers who have delivered an important research contribution into understanding brain disorders and the treatment of these.

Maartje Veeneman has won the second prize of the PhD student competition at the Figon Medicines Days 2008 for her talk "Striatal substrates of cocaine reinforcement".

Rudolf Magnus Graduate School Certificate

The Director and the Research Training Committee of the Graduate School took pleasure in presenting the Rudolf Magnus Graduate School Certificate to the following Doctors: Maartje Raaijmakers (October 30, 2008), Imke van Kooten (November 6, 2008), Jiska Peper (November 20), Heval Özgen (November 28)

agenda and announcements

March 16-22, 2009 Brain Awareness week
http://www.brainawarenessweek.nl/

March 18, 2009 CSCA
Chantal Kemner
'From Neuronal connection to social interaction: perceptual integration in the autistic brain'
Doelenzaal, Singel 421-427, Amsterdam
16.00hr
more information:
http://www.csca.nl/portal/site/csca/page/aeb5aa57-a0f6-478c-00f6-06c55b8c6d75

March 20, 2009 FC Donders Lecture
Doug Crawford (York University, Canada)
'Neural Mechanisms for Donders' law in 3-D Gaze Shifts'
Linnaeusgebouw (LIN6), Heydendaalseweg 137, Nijmegen
15.00hr-17:00hr and free drinks
more information: a.vink@donders.ru.nl

March 24/25, 2009 International Workshop
Multimodal Imaging in Cognitive Neuroscience
Donders Centre for Cognitive Neuroimaging, Radboud University Nijmegen
More information:
http://www.ru.nl/donders/home/agenda/multimodal/

March 25, 2009 Research lunch psychiatry
aula psychiatry, UMC Utrecht
12.00hr -13:00h r, lunch provided
more information: i.sommer@umcutrecht.nl

March 27, 2009 Helmholtz lecture
Richard Mooney (Duke University, USA)
'Learning to communicate: neural mechanisms for learned birdsongs'
contact, Veronica Maassen, helmholtz@fss.uu.nl

March 29, 2009 FC Donders Lecture
Nancy Bonini (University of Pennsylvania, USA)
Linnaeusgebouw (LIN6), Heydendaalseweg 137, Nijmegen
15.00hr-17:00hr and free drinks
more information: a.vink@donders.ru.nl

April 22, 2009 Research lunch psychiatry
aula psychiatry, UMC Utrecht
12.00hr -13:00hr, lunch provided
more information: i.sommer@umcutrecht.nl

April 20/21, 2009 Summerschool RMI
Hotel Van der Valk 'de Cantharel', Apeldoorn

April 21/22, 2009 Mind the brain symposium
Student symposium MSc Neuroscience and Cognition
Keynote speakers: Barry Everitt and Johan Wagemans
Blue lecture hall
More information: www.mindthebrain.org

April 24, 2009 Helmholtz lecture
Jos Eggermont (University of Calgary, Canada)
'Abnormal acoustic environments cause plastic changes in adult auditory cortex learned'
contact, Veronica Maassen, helmholtz@fss.uu.nl

May 12-14, 2009 Academy Colloqium
Nutrition, Metabolism and the Brain
Kloveniersburgwal 29, Amsterdam
More information: martine.wagenaar@bureau.knaw.nl

May 13, 2009 CSCA
Francisco Barchelo (University of the Balearic Islands, Spain)
'Uncertainty, cognitive control and the brain'
Doelenzaal, Singel 421-427, Amsterdam
16.00hr
more information:
http://www.csca.nl/portal/site/csca/page/aeb5aa57-a0f6-478c-00f6-06c55b8c6d75

May 13, 2009 Swammerdam lecture
Hannah Monyer, (University of Heidelburg, Germany)
'Molecular and functional studies of GABAergic interneurones at the cellular and network level'
more information: http://www.onwa.med.vu.nl/swammerdam