

14th PhD Annual Meeting

**Graduate School Neurosciences
Amsterdam**

&

**Rudolf Magnus Graduate School
of Neuroscience**

November 22nd and 23rd, 2007

Woudschoten Conference Center, Zeist

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Cover: Martijn van Roover

Dear PhD student,

Welcome to the 14th Annual Meeting of PhD-students of the Graduate School Neurosciences Amsterdam and the Rudolf Magnus Graduate School of Neuroscience Utrecht at the Conference Center Woudschoten in Zeist.

This meeting is organized for and by PhD-students and offers the opportunity to present work in a friendly and informal atmosphere, to meet other PhD-students from both schools, and to get acquainted with each other's work. PhD-students in their 1st and 2nd year will present their work as a poster, PhD-students in their 3rd year will present a blitz-presentation in addition to a poster, and PhD-students in their 4th year will give an oral presentation.

The two-day program includes research topics on both fundamental and clinical neuroscience. The meeting is also intended to learn how to present one's work to a wide audience. In order to improve your presentation skills, there will be a short plenary evaluation of the presentations after each oral session. In an attempt to get the best out of you, the best poster, the best blitz-presentation and the best oral presentation will be awarded. The best poster will be chosen by a 'poster committee', chaired by Robbert Smit, an external expert on design and layout, whereas the best blitz-presentation and the best oral presentation will be chosen by the audience. Prizes will be awarded on Friday.

We are pleased that the Robert Stickgold will give the Swammerdam Lecture "Sleep, Memory, and Dreams: Beyond Consolidation" on Thursday afternoon. Stickgold is an Associate Professor of Psychiatry at Harvard Medical School in Boston and he is an eminent sleep researcher. He has provided definitive evidence that sleep is important in learning and memory consolidation. It is a great honour to have him as a speaker at the 2007 PhD-student meeting.

The organizers are grateful to the senior scientists who are coming to the meeting to guide the sessions.

We hope that this PhD meeting in Woudschoten will give you a scientifically satisfactory exchange as well as a pleasant stay.

The organizing committee:

Sanne Boesveldt
Els Borghols
Elly Hol
Gijs Kooij
Maurice Magnée
Els Møst
Charlotte Oomen
Jeroen Pasterkamp
Marleen Sta
Jelte Wouda
Tim Ziermans

Program Annual Meeting 2007 Thursday, 22 November

09.00 - 09.50 Registration / coffee and tea

09.50 - 10.00 Words of welcome

Retreat committee 2007

Didactic comments

Marian Joëls

10.00 - 11.10 **Clinical studies (page 12-15)**

chair: Wouter Staal

Sanne Boesveldt

Olfactory dysfunction in Parkinson's disease: what is the best olfactory test to discriminate between patients and control?

Maartje Raaijmakers

Incredible years; preliminary results of a preventive intervention for preschoolers at risk of conduct disorder.

Ingrid van Rooy

Vestibular evoked myogenic potentials.

Dirk-Wouter Smits

Clinical assessment of selective motor control in children aged 5 – 7 years with cerebral palsy.

11.10 - 11.30 Printers market with coffee and tea

11.30 – 12.25 **Session 2: Hippocampus (page 16-18)**

chair: Jan Gorter

Niels van Strien

The role of the medial temporal lobe in crossmodal memory: a functional mri study.

Jeroen Dudok

Serotonin inhibits serotonergic projections from raphe nucleus to hippocampus ex vivo.

Zhenwei Pu

Can stress be "timed"?

12.25 - 13.15 Lunch and printers market

13.15 - 13.35 **Blitz Session I**

chair: Marian Joëls

13.35 - 14.50 **Poster Session I (page 34-99 alphabetically) / Printers market**

Chairs: Elly Hol, Bas Neggers, Eus van Someren, Wouter Staal, Taco de Vries, Ysbrand van der Werf

14.50 - 15.35 Printers market

15.35 - 16.30 **Session 3: Brain imaging (page 19-21)**

chair: Bas Neggers

Maqsood Yaqub

Quantification of [¹⁸F]]FDDNP studies.

Saskia Wolfensberger

Evaluation of [¹¹C]R116301 as PET tracer of the NK1 receptor: a test-retest study in human subjects.

Ellemarije Altena

Prefrontal functioning recovered: brain imaging and behavioural results of verbal fluency in insomnia before and after sleep therapy.

16.40 - 17.50 **Swammerdam Lecture (page 11)**

Sleep, memory, and dreams: beyond consolidation.

Robert Stickgold, PhD, Assoc. Professor of Psychiatry from the Center for Sleep and Recognition, Harvard Medical School, Boston, USA

18.00 - 20.00 Dinner

20.00 - 21.00 **Scientific quiz**

Program Annual Meeting 2007 Friday, 23 November

08.30 - 09.30 Breakfast

Didactic comments

Huib Mansvelder

09.30 - 10.40 **Electrophysiology (p. 22-25)**

chair: Arjen Brussaard

Marloes Joossen

Percutaneous exposure to VX: clinical signs, effects on brain acetylcholine levels and EEG.

Eunjeong Lee

The rat medial prefrontal cortex in control of attention: changes in firing patterns induced by crossmodal distraction.

Maurice Magnée

The importance of multisensory integration in social interaction: EEG evidence from individuals with autism.

Christiaan Stronks

Combined electric and acoustic stimulation in the cochlea of the guinea pig.

10.40 - 11.00 Coffee and tea

11.00 - 12.10 **Neurodegeneration and regeneration (p. 26-29)**

chair: Elly Hol

Hilde Krol

Ataxin-1 accumulations in SCA1 do not resemble 'classical' polyglutamine aggregates.

Harold Mac Gillavry

The transcription factor NFIL3 is an intrinsic regulator of successful neuronal regeneration.

Martijn Agterberg

Neurotrophic treatment of the auditory nerve in deafened guinea pigs.

Maria Macedo

The role of SUMOylation of DJ-1 in Parkinson's disease.

12.10 - 13.00 Lunch

13.00 - 13.20 **Blitz Session II**

chair: Huib Mansvelder

13.20 - 14.50 **Poster Session II (page 34-99 alphabetically)**

Chairs: Arjen Brussaard, Elly Hol, Martien Kas, Huib Mansvelder, Jeroen Pasterkamp, Louk Vanderschuren

14.50 - 16.00 **Endophenotypes (page 30-33)**

chair: Martien Kas

Daniel van Grootheest

Heritability of obsessive-compulsive symptoms.

Daniëlle Counotte

Adolescent nicotine exposure impairs cognitive function in adulthood.

Imke van Kooten

Neurons in the fusiform gyrus are fewer and smaller in autism.

Marijke Laarakker

Genetic dissection of mouse anxiety-related behavior.

16.00 - 16.10 Poster Award

Robbert Smit & Karin Boer

16.10 - 16.20 Blitz and Oral Presentation Award

16.20 - 16.30 Closing remarks

Retreat committee 2007

Blitz Session I

Marijke de Backer
Ofir Betsalel
Karin Boer
Nienke Dekker
Duco Endeman
Judith Gillis
Carlijn Hoekstra
Maurits van der Meer
Els Møst
Charlotte Oomen
Alicia Sanz Sanz
Marijn van Wingerden

22 November, 13.15 - 13.35

chair: Marian Joëls

Blitz Session II

Hendrik Bremer
Cathrin Canto
Gijs Kooij
Cédric Koolschijn
Jasper Poort
Thomas Rietkerk
Maartje Veeneman
Floris van Velden
Elly Vereyken
Tim Ziermans

23 November, 13.00 - 13.20

chair: Huib Mansvelder

Poster Session I

22 November, 13.35 - 14.50

Group A

- 1) Maria Alves dos Santos
Do Pitx3 and En1 interact in the mesodiencephalic dopaminergic (mdDA) system?
- 2) Marijke de Backer
Determination of optimal adeno-associated viral vector serotypes for transgenesis in the lateral hypothalamus of the rat.
- 3) Simone van den Berge
GFAP-delta expression in subventricular zone astrocytes.
- 4) Ofir Betsalel
Detection of low-level somatic and germline mosaicism by denaturing high performance liquid chromatography in a EURO-MRX family with SLC6A8 deficiency.
- 5) Karin Boer
Molecular pathogenesis of tuberous sclerosis complex in patients with intractable epilepsy.
- 6) Marieke de Boer
Towards neural coding of attentional processes in mouse prefrontal cortex.

Group C

- 13) Nienke Dekker
Implicit and explicit expectations of cannabis use in patients with schizophrenia and related disorders.
- 14) Kelly Diederer
Comparing auditory verbal hallucinations to inner speech in schizophrenia; an fMRI study.
- 15) Ruben van Doorn
The sphingolipid rheostat influences brain endothelial integrity.
- 16) Duco Endeman
Cones perform a nonlinear transformation on a natural time series of intensities.
- 17) Judith Gillis
Visualising intracellular aggregate formation and clearance using non-degradable fluorescent protein fragments.

- 18) Asiya Giniatullina
Calcium-dependent cross-linking of phospholipid membranes by synaptotagmin-1.

Group D

- 19) Felisa van Hasselt
The influence of maternal care on long-term potentiation in the adult rat dentate gyrus.
- 20) Erika van Hell
Differential effects of cannabis and nicotine on the human reward system.
- 21) Ellen Hessel
Screening of the chromosome substitution strain panel to identify febrile seizure susceptibility genes.
- 22) Carlijn Hoekstra
Hydrochlorothiazide induced tinnitus: a case report.
- 23) Elisa Hoekstra
Identifying the specific role of transcription factors Lmx1a and Lmx1b in the genetic cascade leading to mdDA development.
- 24) Willem Huijbers
When remembering hinders learning.

Group F

- 31) Joost Meekes
Memory after temporal lobectomy in children.
- 32) Maurits van Meer
Electrophysiological basis of functional MRI signals in rat models of permanent and transient cerebral ischemia.
- 33) Marjolijn Mertz
Type III neuregulin 1 signaling in prefrontal cortical neurons.
- 34) Els Møst
Circadian temperature rhythms in elderly with cognitive dysfunctions.
- 35) Jurgén Mourik
Estimation of image derived input functions using a reconstruction based partial volume correction algorithm: methodology and evaluation in [¹¹C]flumazenil studies.
- 36) Charlotte Oomen
Early maternal separation induces prominent gender differences in neurogenesis without affecting newborn cell survival.

Group H

- 42) Nico Romeijn
Selective slow-wave-sleep deprivation induces lapses of attention in psychomotor vigilance tasks.
- 43) Amber Salomons
Repeated exposure to a novel environment; evaluating the adaptive capacity in the BALB/c and 129/J mouse strain.
- 44) Alicia Sanz Sanz
Crb2 cKO, what is the role of Crb2 in the retina?
- 45) Sebastian Schagen
Long-term delay of puberty by treatment with GnRH-analogues and the effect on bone mineral density (BMD) in transsexual adolescents.
- 46) Thomas Scheewe
Physical activity and cardiovascular fitness in patients with schizophrenia.

Group K

- 57) Elisabeth Wansink
M1 and M2 receptor activation alters synaptic transmission of the layer 5 medial prefrontal cortex.
- 58) Marijn van Wingerden
Role of NMDA-receptors in baseline and task-related firing of orbitofrontal cortex neurons during a 2-odour discrimination task.
- 59) Jelte Wouda
β-adrenoreceptor mediated inhibition of long-term alcohol-related memory reconsolidation.

- 60) Femke Wouters
Brain development and brain functioning in the clinical management of transsexual adolescents.
- 61) Jiun Youn
Social defeat as an ethological model for the generation of depression-like symptoms in mice.

Poster Session II

23 November, 13.20 - 14.50

Group B

- 7) Rhea van de Bospoort
Characteristics of the C2 domains of Doc2B.
- 8) Olga Braams
What makes parents happy after hemispherectomy of their child?
- 9) Hendrik Bremer
A comparison of the vestibulotoxic effects of gentamicin and co-administration of kanamycin and furosemide in guinea pigs.
- 10) Jurjen Broeke
The role of neurotransmitter secretion during axon outgrowth on growth cone dynamics.
- 11) Nutabi Camargo
Screening for astrocyte derived signals involved in neurite outgrowth and synaptogenesis.
- 12) Cathrin Canto
Rate-to-phase transform in layer II principal neurons of the rat medial entorhinal cortex.

Group E

- 25) Anne Kan
Potential role of the immune system in human temporal lobe epilepsy.
- 26) Gijs Kooij
Blood-brain barrier characteristics in MS lesions.
- 27) Cédric Koolschijn
The effects of antipsychotic medication on hippocampal volume changes in schizophrenia.
- 28) Joanna Korecka
Parkinson disease: from dysregulated human brain targets towards novel therapeutics.
- 29) Cathalijn Leenaars
12 hours of full sleep deprivation by means of forced locomotion decreases the motivation for food reward.
- 30) Hemi Malkki
Characterizing pinky and the brain: operant learning as a tool for behavioural screening and QTL mapping of recombinant inbred mice.

Group G

- 37) Jasper Poort
Task difficulty and the encoding of behavioural relevance in primary visual cortex.
- 38) Priyanka Rao
Differences in memory consolidation in inbred mouse strains.
- 39) Margreet Ridder
MLC1 is associated with the Dystrophin-Glycoprotein Complex at astrocytic endfeet.
- 40) Thomas Rietkerk
The genetics of symptom dimensions of schizophrenia: review and meta-analysis.
- 41) Laura Rigter
The effect of maternal care on the development of cortical layer 2/3 pyramidal neurons: a link with reelin.

Group I

- 47) Kasper Roet
Identification of molecular targets for improvement of cell graft function for treatment of spinal cord injuries.
- 48) Sabine Schmitz
Role of MUNC13 in neuronal dense core vesicle release.
- 49) Eelke Snoeren
Novel animal model for female sexual dysfunction.

- 50) Jean-Pierre Sommeijer
The role of the GABA_AR subunit α 1 and the GABAergic inhibitory system in molecular visual plasticity.
- 51) Marleen Sta
Role of macrophages in peripheral nerve degeneration.

Group J

- 52) Maartje Veeneman
Striatal substrates of cocaine taking.
- 53) Floris van Velden
Accuracy of various 3D-OSEM versus 3D-FBP reconstructions of HRRT PET studies.
- 54) Elly Vereyken
An in vitro model for specific de- and remyelination using whole brain spheroid culture.
- 55) Nelleke Verhave
Tower and hourglass: two motor behaviour tests for marmoset.
- 56) Mariska Verlaan
Reward-sensitivity is stronger in standard housed male rats than in enriched housed male rats, which is independent of strain.

Group L

- 62) Patrick de Zeeuw
Profiling ADHD using longitudinal sMRI and DTI: methods and measures.
- 63) Tim Ziemans
Before psychosis: a comparison of brain volumes in adolescents at ultra high risk and typically developing subjects.
- 64) Esther van der Zwaal
Olanzapine-induced weight gain: an animal model using male rats.
- 65) Rana Al Hussainy
Synthesis of ¹⁸F-labelled cubyl-WAY.
- 66) Hans Buiters
Synthesis and evaluation of [¹¹C]AF150(S), a potential new agonist PET ligand for the m1ACh-R.

ABSTRACTS

Swammerdam Lecture prof.dr. Robert Stickgold

For oral presentations: in order of presentation

For poster presentations: in alphabetical order

SWAMMERDAM LECTURE

TITLE

SLEEP, MEMORY, AND DREAMS: BEYOND CONSOLIDATION

AUTHOR

Robert Stickgold

DEPARTMENT/INSTITUTE

Assoc. Professor of Psychiatry, Center for Sleep and Cognition, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

ABSTRACT

Sleep plays an important role in the offline processing of recent memories. At the most basic level, sleep can stabilize and strengthen memories, leading to improved performance on numerous tasks after a night of sleep. But more recent findings indicate that sleep also integrates recent memories into complex networks of older memories. In doing so it identifies the most important aspects of recent memories, sometimes identifying patterns and regularities not perceived during waking, and always placing the memory within the context of older memories, thereby interpreting the new memory and defining its meaning. Evidence for these sleep functions will be presented, and the role of dreaming in these processes will be explored.

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TITLE**OLFACTORY DYSFUNCTION IN PARKINSON'S DISEASE: WHAT IS THE BEST OLFACTORY TEST TO DISCRIMINATE BETWEEN PATIENTS AND CONTROLS?****AUTHORS**

Sanne Boesveldt¹, R.J.O. de Muinck Keizer¹, D.L. Knol², E.Ch. Wolters¹, H.W. Berendse¹

DEPARTMENT/INSTITUTE

¹Department of Neurology, VU University Medical Center, Amsterdam, ²Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam

ABSTRACT**Introduction**

An impairment of the sense of smell is among the earliest non-motor signs of Parkinson's disease (PD) and may prove useful in future screening strategies. The sense of smell comprises a number of identifiable olfactory functions that can be assessed by psychophysical testing. The aim of the present study was to determine which (combination of) olfactory test(s) is best in distinguishing between PD patients and controls.

Methods

The study population consisted of 50 PD patients (Hoehn and Yahr stages I-III) and 50 control subjects, all aged between 50-78 years. The Sniffin' Sticks test battery was used to measure various aspects of olfactory function. *Odour detection threshold* was assessed using a single-staircase, three-alternative forced-choice procedure, with a 1:2 dilution series of sixteen stages. Subjects had to identify the odour-containing pen when presented with three pens, two containing the solvent and one the odorant (score 0-16). In the *odour discrimination* task, subjects were presented with 32 triplets of odorants and asked to select the odd odour out of each triplet. *Odour identification* was measured by presenting 32 odorants in a multiple (4)-forced choice format. In each task, olfactory scores were defined as the total number of correct answers. In the *odour recognition memory* task, subjects were presented with 8 target odorants and were asked to memorize them. After a short break, 16 odours were presented (8 target odours, 8 distracters), and the subject was asked whether the odour had been smelled before. The total score was calculated as hit rate (0-8) minus false alarm rate (0-8).

Results and conclusion

Preliminary results indicate that combining tests assessing different olfactory functions improves the diagnostic value of olfactory testing to a greater extent than increasing the number of trials within a test of a single olfactory function. Receiver operating characteristic (ROC) curves based upon sensitivity and specificity estimates for each (combination of) tests will be presented at the meeting.

Keywords: Parkinson's disease, olfaction, clinical

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TITLE**INCREDIBLE YEARS; THE PRELIMINARY RESULTS OF A PREVENTIVE INTERVENTION FOR PRESCHOOLERS AT RISK OF CONDUCT DISORDER****AUTHORS**

Maartje Raaijmakers, Jocelyne Posthumus, Walter Matthys, Herman van Engeland

DEPARTMENT/INSTITUTE

Child- & Adolescent Psychiatry, University Medical Centre Utrecht, Rudolf Magnus Institute for Neuroscience, Utrecht

ABSTRACT

Childhood aggression is escalating, and at younger ages. Aggressive behaviour or disruptive behaviour problems often develop into the most prevalent disorders in child- and adolescent psychiatry; Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD). These disorders have negative consequences later in life, e.g. criminal activities, substance abuse, unemployment, academic failure, which bring high costs to society. Therefore, research on the prevention and treatment of aggression is vitally important. The emergence of early onset Disruptive Behaviour Disorders (DBD) in preschool children is stable over time and appears to be the most important risk factor predictive of antisocial behaviour in adolescence. Since treatment of aggression becomes increasingly difficult and more costly as children grow older, it seems both pragmatic and cost-effective to offer treatment and prevention efforts during the toddler and preschool years.

Parent management training is the most effective treatment for reducing aggression in young children (2 – 5 years). In this study, the preventive effect of the Parent training from the Incredible Years Training Series designed by Carolyn Webster-Stratton is evaluated. This program aims to enhance parent management skills of the parents and to reduce the aggressive behaviours of the child.

In the present study, 144 preschool children from the province of Utrecht who are at risk for the development of disruptive behaviour disorders were selected. A matched control design was used to compare the intervention group (N = 72) to a group of parents with children who are also at risk, but who are not receiving training (only care-as-usual) (N = 72). Several measures were used to assess parenting and child behaviour; Child Behaviour Checklist 1½-5, Eyberg Behaviour Inventory, Diagnostic Interview Schedule for Children, Parenting Practices Interview and the Daily Discipline Interview. Preliminary pre-post-data on these measures will be presented.

KEY WORDS: Parent management training, preschoolers, disruptive behaviour disorders

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TITLE
VESTIBULAR EVOKED MYOGENIC POTENTIALS

AUTHORS

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ABSTRACT

Dizziness is one of the most common complaints of patients of the ear – nose –throat specialist. The lifetime prevalence of vertigo is 10.3% in women, and 4.3% in men. Dizziness can be defined as ‘the sensation of motion when no motion is occurring relative to gravity’. Vertigo is a special case of dizziness, often characterised by a spinning sensation. Vertigo is associated with loss of vestibular function. The vestibular organ is a complex organ located in the inner ear and consists of five parts. Angular accelerations are detected by the three semicircular canals. Linear accelerations are detected by the otolith organs, called the sacculus and utriculus.

Treatment options are scarce; this is partly due to limited diagnostic tools available for evaluation of dizziness patients. For years electronystagmography (ENG) was the only objective vestibular diagnostic test to assess the function of one part of the vestibular organ (the horizontal semicircular canal). A recently developed, non-invasive, function test is the “vestibular evoked myogenic potential” (VEMP). The VEMP test can assess the function of the sacculus and the inferior vestibular nerve, thus providing information on otolith function.

VEMPs can be elicited by providing loud sounds to the inner ear. As a result a reflex, which is assumed to originate in the sacculus, is transmitted to the motor neurons of the sternocleidomastoid muscle. The VEMP response is recorded ipsilaterally from the monaurally presented stimulus, using symmetric sites over the sternocleidomastoid muscle.

So far, numerous studies on VEMP testing have been published. However, no consensus on the method of measurement has been reached, nor are there normative data available. To make VEMP measurement applicable in the diagnostic work-up of patients with vertigo the Netherlands, the aim of our study is to obtain normative data. Adult volunteers were invited to participate in the study.

Standardised recording procedures were used. The stimulus intensity was started at 130dB SPL and was decreased until the threshold was established (tone bursts, 500 Hz, rise/fall time 2 ms, plateau 2 ms, repetition rate 5 Hz). Normative data were obtained for several VEMP parameters (latencies, amplitude and threshold). Measurements were repeated three times to assess reliability. Overall results and results according to age categories will be presented.

KEY WORDS: Inner ear, vertigo, diagnostic, VEMP

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TITLE

CLINICAL ASSESSMENT OF SELECTIVE MOTOR CONTROL IN CHILDREN AGED 5 - 7 YEARS WITH CEREBRAL PALSY

AUTHORS

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ABSTRACT

Objective: To explore the inter-tester reliability for clinical assessment of Selective Motor Control (SMC) in children aged 5 - 7 years with Cerebral Palsy (CP).

Methods: 22 children (mean age 6,5 [SD 1,0] years; 14 male) with spastic CP (14 unilateral, 8 bilateral, severity across all GMFCS levels) were assessed. Two instruments were selected for clinical assessment of SMC: 1) a five points scale for muscle activation in ankle dorsiflexion by Boyd & Graham¹ and 2) a three points scale for general joint movement by Trost². To our knowledge, the latter does not have a published protocol, so we developed it for ankle dorsiflexion, and also for knee and hip movements. Each child was assessed by two independent testers with a time interval of 1 hour. For both instruments weighted Cohen's Kappas were calculated per joint.

Results: For ankle dorsiflexion left and right, weighted Kappas were 0.61 and 0.72 ('Boyd & Graham' scale) and 0.65 and 0.89 ('Trost' scale). Besides, for knee and hip movements ('Trost' scale), weighted Kappas ranged from 0.71 to 0.79.

Conclusions: This study shows that selective motor control can reliably be assessed in children aged 5-7 years with CP: for ankle dorsiflexion with substantial reliability agreement with the 'Boyd & Graham' scale (muscle activation) and for ankle, knee and hip movements with substantial to almost perfect agreement with the 'Trost' scale (joint movement).

References

- 1) Boyd R.N. & Graham H.K. Objective measurement of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy, *Eur J Neurol* 8 (1999) (Suppl 6), pp. S23-S35.
- 2) Trost J. Physical assessment and observational gait analysis. In: Gage J.R., Editor, *The treatment of gait problems in cerebral palsy.*, Mac Keith Press, London (2004), pp. 71-89.

KEY WORDS: cerebral palsy, selective motor control, clinical assessment

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TITLE**THE ROLE OF THE MEDIAL TEMPORAL LOBE IN CROSSMODAL MEMORY:
A FUNCTIONAL MRI STUDY****AUTHORS**

Niels M. van Strien¹, H. Lehn², M.P. Witter³

DEPARTMENT/INSTITUTE

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ABSTRACT

Declarative memory, that is the conscious recollection of facts and events, comprises mostly information from different sensory modalities. This type of memory is known to rely on a neuronal network within the medial temporal lobe (MTL). Specifically, the hippocampal formation and the adjacent parahippocampal region are thought to be of pivotal importance to learning and memory. The hippocampus receives input from the parahippocampal region, which in turn receives information from all sensory cortical domains. Moreover, the parahippocampal region is the main intermediary to relay hippocampally processed information back to sensory cortical domains. A characteristic feature of conscious recall is that input arising from only one single sensory domain, for example olfaction, may trigger the conscious recollection of an episode with all of its multimodal features. Sparse animal experimental data indicated that this characteristic crossmodal learning and memory most likely is also mediated by structures in the MTL. However, not much is known about how the MTL contributes to crossmodal memory. In this study we aimed to discover which areas in the MTL are specifically involved in retrieving crossmodal information from memory. We taught subjects unique associations between tactile, auditory and spatial stimuli on the one hand and a unique visual object on the other hand. Subjects learned several of these unique crossmodal stimulus groups. Preliminary results show the involvement of the perirhinal cortex in crossmodal associations, indicating that retrieval of crossmodal memory is more strongly dependent on the parahippocampal region than on the hippocampal formation.

KEY WORDS: Hippocampus, crossmodal; memory; association; parahippocampus

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TITLE**SEROTONIN INHIBITS SEROTONERGIC PROJECTIONS FROM RAPHE NUCLEUS TO HIPPOCAMPUS EX VIVO****AUTHORS**Jeroen J. Dudok, A.J. Groffen, P. Voorn, M.P. Witter, M. Verhage**DEPARTMENT/INSTITUTE**

Center for Neurogenomics and Cognitive Research (CNCR), Department of Functional Genomics, Vrije Universiteit Amsterdam, Amsterdam

ABSTRACT

The serotonin system is involved in regulating a wide variety of processes and in psychopathological processes such as anxiety and depression. Previously it has been shown in non-mammalian cells that serotonin can influence outgrowth and connectivity of the serotonin system. Therefore, here we investigated whether also in a mammalian system serotonin or antidepressive drugs have an effect on the outgrowth and connectivity of the serotonin system. To this end we have established an organotypic slice co-culture model system consisting of a dorsal raphe nucleus and a hippocampal slice. We have used this model system to study the effect of chronic application of serotonin or antidepressive drugs on serotonergic outgrowth and connectivity. Moreover, we have also used live cell imaging on serotonergic growth cones to study the effect of acute application of serotonin on outgrowth. Here, we will provide evidence that serotonin inhibits outgrowth of serotonergic projections, which affects serotonergic network connectivity.

KEY WORDS: Serotonin, organotypic, outgrowth, connectivity, imaging**TELEPHONE-NUMBER:** 020-5986931**E-MAIL-ADDRESS:** jeroen.dudok@cncr.vu.nl

TITLE**CAN STRESS BE “TIMED”?****AUTHORS**Zhenwei Pu, Harm Krugers, Marian Joëls**DEPARTMENT/INSTITUTE**

Center for Neuroscience, Swammerdam Institute for Life Sciences, University of Amsterdam

ABSTRACT

Generally, emotionally-laden facts are better remembered. These facts, many of which are stressful, seem to facilitate memory formation. However, deleterious effects of stress on memory are otherwise observed. Striving to disentangle this concept complex, we have attempted to address this issue from a unique angle by identifying the timing factor in stress-induced hormonal actions. Using an in vitro animal model, we could monitor the synaptic strength between hippocampal dentate gyrus synapses. This synaptic strength was subject to regulations by beta-adrenergic agonist and corticosterone. As acute administration of beta-adrenergic agonist enhanced it, corticosterone acted bidirectionally within different time domains. Corticosterone can either facilitate beta-adrenergic action or suppress its regulation, depending on when it is applied in regard to the onset of noradrenergic activity. This study supplements the previous ones in the CA1 region that are indicative of the timing effects on synaptic plasticity per se. These studies encourage searching for further evidence of the biphasic glucocorticoid regulation of memory, which is determined by timing-relevant mechanisms, i.e. a rapid, nongenomic one and a delayed, genomic one. Further steps are taken and favourable proofs are systematically acquired in other brain regions and at different functional levels.

KEY WORDS: Glucocorticoids, memory, timing, hippocampus**TELEPHONE-NUMBER:** 020-5257646**E-MAIL-ADDRESS:** zpu@science.uva.nl

TITLE
QUANTIFICATION OF [¹⁸F]FDDNP STUDIES

AUTHORS

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ABSTRACT

In the present study kinetic and semi-quantitative methods for analysing human [¹⁸F]FDDNP studies were evaluated using both simulations and clinical data: plasma input models (single-tissue, two-tissue irreversible and two-tissue reversible compartment models), simplified (SRTM) and full (FRTM) reference tissue models, standard uptake value ratios with reference (SUV_r). In addition, two models were added based on modified two-tissue reversible model (2T4k) to include an additional single-tissue compartment for metabolites (2T1M and 2T1M_{fvtm}, the latter fixing volume of distribution of metabolites). 2T4k, 2T1M and 2T1M_{fvtm} were also used to estimate BP_{ND} indirectly, i.e. using volume of distribution ratio's with the cerebellum -1.

2T4k showed accurate outcomes during conventional simulations, however, BP_{ND} estimates were poor for relatively low regional delivery (K_1) levels and if metabolites entered the simulated brain tissue. In general, indirect plasma input models, showed much better accuracies and precisions, but only indirect 2T1M_{fvtm} models showed stable results if metabolites entered brain. SRTM outcomes were comparable in both conventional and with including metabolite compartment simulations showing a constant bias for BP_{ND} , with better precisions than indirect 2T4k and 2T1M_{fvtm} and was in general better than FRTM, in terms of accuracies and precisions in BP_{ND} . SUV ratios, direct 2T4k, SRTM and FRTM were most affected by regional delivery differences. However, SUV ratio methods showed good accuracies but worse COV than SRTM and were also more dependent on V_b , with additional needs for an accurate time interval.

Akaike criterion preferred 2T1M models above conventional plasma input models and preferred SRTM above FRTM for clinical data. The numbers of physiological extreme outliers in the outcomes of all models were acceptable, except for FRTM and 2T1M_{fvtm}. Good correlations with BP_{ND} SRTM were only seen in FRTM, SUV_{r40-60} (over 40-60 minutes), indirect 2T1M and indirect 2T1M_{fvtm}. The indirect 2T1M models correlated much better with BP_{ND} SRTM than conventional indirect 2T4k, suggesting that metabolites could enter brain tissue.

In summary, SRTM is the methods of choice for quantitative analysis of [¹⁸F]FDDNP even if it is unclear if metabolites do or do not enter brain, provided that the metabolite volume of distribution is relatively constant across the brain and between the subjects as clinical results suggest.

KEY WORDS: [¹⁸F]FDDNP, PET, SUV, reference tissue model, plasma input model, metabolites

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TITLE

EVALUATION OF [¹¹C]R116301 AS A PET TRACER OF THE NK1 RECEPTOR: A TEST-RETEST STUDY IN HUMAN SUBJECTS

AUTHORS

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ABSTRACT

Introduction

R116301 is an orally active, potent and selective non-peptide NK1 receptor antagonist. In a previous study [1], size and presence of the specific signal of [¹¹C]R116301 was demonstrated using a blocking study. Based on the striatum to cerebellum ratio, a specific signal of around 20-50% was found. To assess [¹¹C]R116301 further as an NK1 receptor ligand, the purpose of the present study was to assess test-retest variability of [¹¹C]R116301 binding.

Methods

Studies were performed in 8 normal controls. Each study consisted of two [¹¹C]R116301 scans, 5 hours apart. Individual scan sessions consisted of a 2D transmission scan and a 90 minutes dynamic 3D emission scan following intravenous administration of ~390 MBq [¹¹C]R116301 [2]. A region of interest comprising whole striatum (the structure with the highest density of NK1 receptors) was defined on an individual MRI scan and projected onto both co-registered PET scans. Cerebellum was used as reference tissue. Striatum to cerebellum ratios (60-90 minutes post injection) were used as outcome parameter. In addition, striatum BP was obtained using Receptor Parametric Mapping (RPM), the basis function implementation of the simplified reference tissue model [3]. Data could not be analysed with arterial input compartment models due to severe stickiness of the tracer.

Results

Equilibrium was reached relatively early after injection, and striatum to cerebellum ratios were almost identical for the intervals 20-90 and 60-90 minutes. Test-retest results of striatum to cerebellum ratios were very tight (range 0.97-1.06), showing an average difference of 3% between scans. However, this ratio contains both specific and non-specific components. For the specific component (i.e. by subtracting 1 from the ratios), the average difference between the two scans was 10% (excluding subject 3, where no specific signal was observed). This was similar to the 9% average difference in BP between the two scans as measured with RPM.

Conclusion

Test-retest variability of striatum to cerebellum ratios was excellent (3%). Despite the relatively high level of non-specific binding, test-retest variability of specific binding (BP) remained acceptable (10%). The large variation in specific signal between subjects needs to be addressed in future studies.

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3. Gunn *et al.* (1997) NeuroImage 6: 279-287.

KEY WORDS: PET, NK1 receptor, [C-11]R116301

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TITLE**PREFRONTAL FUNCTIONING RECOVERED: BRAIN IMAGING AND BEHAVIOURAL RESULTS OF VERBAL FLUENCY IN INSOMNIA BEFORE AND AFTER SLEEP THERAPY****AUTHORS**

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ABSTRACT

Sleep deprivation is known to affect prefrontal functioning, but whether chronic insomnia has the same effect on prefrontal functioning was not known so far. By applying verbal fluency tasks in fMRI, we show that patients suffering from strictly diagnosed psychophysiological insomnia for more than 2 years, show less prefrontal activation in brain areas normally activated in this task by healthy age matched controls. After applying intense sleep therapy, involving combined cognitive behavioral therapy, sleep restriction, sleep hygiene measures, bright light, physical activity and temperature interventions, we found that 1) the behavioural performance improved and 2) brain activation patterns returned to normal, in contrast to insomnia patients who were assigned to a waiting list condition for the same period. Improved prefrontal-cortex dependent cognitive performance and increased prefrontal brain activation suggest reversible hypofrontality in chronic insomnia.

KEY WORDS: Prefrontal cortex, functional imaging, insomnia

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TITLE**PERCUTANEOUS EXPOSURE TO VX: CLINICAL SIGNS, EFFECTS ON BRAIN ACETYLCHOLINE LEVELS AND EEG****AUTHORS**

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ABSTRACT

The nerve agent VX has a variable and delayed absorption through the skin, which may have implications for treatment regimens. In the present study, central and peripheral effects of percutaneous VX intoxication were investigated in hairless guinea pigs. Although onset times of clinical signs varied considerably, the relative onset times of signs of poisoning were shown to have a predictive value for survival time. All animals showed elevation of brain choline levels. Only 2 out of 6 animals demonstrated seizure activity on EEG, which was accompanied by acetylcholine accumulation. The non-seizing animals displayed only marginal increases of acetylcholine levels, but significant changes in all EEG bands. Acetylcholinesterase activity was highly inhibited in brain and diaphragm. The increases in choline levels and EEG effects observed in non-seizing animals probably reflected those of ischemia induced by peripheral effects leading to cardiorespiratory compromise. In conclusion, clinical signs will mainly serve as indicators for the onset and maintenance of treatment in subsequent studies.

KEY WORDS: VX, [O-ethyl S-(2-diisopropylaminoethyl) methylphosphonothioate], acetylcholine, choline, EEG, percutaneous exposure, hairless guinea pig, brain microdialysis

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TITLE**THE RAT MEDIAL PREFRONTAL CORTEX IN CONTROL OF ATTENTION: CHANGES IN FIRING PATTERNS INDUCED BY CROSSMODAL DISTRACTION****AUTHORS**

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ABSTRACT

Control of attention for maintaining relevant information during changing environmental conditions is an essential characteristic of executive function and has been found to be impaired in schizophrenia. Selective attentional processing is thought to be mediated by many cooperating brain areas and pertains not only to selection amongst events in a single sensory modality, but also across different modalities. However, most studies so far have focused on unimodal attentional control, not on the ability to focus on stimuli within a given modality while ignoring stimuli in another one.

We designed a multimodal discrimination task set in a chamber where visual and odor stimuli could be presented to the rat in time-controlled manner and investigated ensemble coding strategies of neurons in the medial prefrontal cortex (mPFC) of freely moving rats using a multi-tetrode recording technique. The learning task required the rat inserted its head into the chamber for 1 sec, during which stimuli could be simultaneously presented (e.g. rose odor and/or a visual pattern). All sessions started with a simple discrimination (SD) protocol requiring a Go/NoGo response to a pair of exemplars in the same sensory dimension. If the rat reached criterion, it was subjected to a compound discrimination (CD) protocol where two new exemplars in different, irrelevant dimension were added to the stimulus pair. In this phase, the rat was required to keep focusing on and discriminating between the two stimuli from the relevant dimension (cf. Birrell and Brown, *J. Neurosci.* 20 (2000), 4320-4324). We hypothesize that mPFC neurons help to minimize cross-modal distraction by participation in focusing attentional process on the relevant dimension.

We analyzed 155 units from 2 rats recorded during odor + visual CD sessions (relevant dimension: odor); 69.7 % of these units were correlated to task events as during SD (stimulus sampling phase: 27.7 %, reinforcement delivery phase: 16.8 % and pre/post-stimulus action phases: 18.7 %, p -value < 0.05; Friedman's test). Comparing CD with SD, we found that most changes in neural firing pattern occurred during the stimulus sampling phase (53% of which, p -value < 0.05; Kolmogorov-Smirnov test). These changes could be subdivided in several classes such as a disappearance of the response after switching from SD to CD (16.3 %), appearance (7%), firing rate increments (2.3%), decrements (25.6%) or changes in response (extension or delay of response (2.3%)), while the overall sampling and Go-NoGo behavior remained unchanged. The results could show involvement of mPFC neurons in control of attention.

KEY WORDS: Multimodal discrimination, multi electrode recording, attentional set shifting

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TITLE**THE IMPORTANCE OF MULTISENSORY INTEGRATION IN SOCIAL INTERACTION: EEG EVIDENCE FROM INDIVIDUALS WITH AUTISM****AUTHORS**

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ABSTRACT**Background**

Integration of information from multiple sensory sources is an important prerequisite for successful social behavior, especially during face-to-face conversation. It has been suggested that communicative impairments among individuals with Autism Spectrum Disorders (ASD) might be caused by an inability to integrate synchronously presented visual and auditory cues.

Methods

We investigated audiovisual integration of speech stimuli among a group of high-functioning adult individuals with ASD and age- and IQ matched controls using electroencephalography, focusing both on early pre-phonological, as well as late phonological integration.

Results

We show dissociation in integrational abilities in the patient group, with a deficit specifically related to the late integration of phonological information.

Conclusions

Among individuals with ASD, the present findings argue for a pattern of impairments on tasks related to complex audiovisual integration, and relative sparing of low-level integrational abilities. This may very well contribute to the communicative disabilities which are typical for the disorder.

KEY WORDS: Multisensory integration, language and communication, autism, EEG, visual, auditory

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TITLE**COMBINED ELECTRIC AND ACOUSTIC STIMULATION IN THE COCHLEA OF THE GUINEA PIG****AUTHORS**H. Christiaan Stronks, Huib Versnel, Vera F. Prijs, Sjaak F.L. Klis**DEPARTMENT/INSTITUTE**

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ABSTRACT

The continuous improvement of the performance of cochlear implants has led to the relaxation of the criteria for candidacy for implantation. Patients with considerable residual low-frequency hearing are nowadays considered for implantation (Kiefer et al., *Audiol Neurotol* 2005). When residual hearing is preserved after implantation, electric hearing via the implant can be supplemented with low-frequency acoustic hearing with an ipsilateral hearing aid. The use of an ipsilateral hearing aid can improve both speech intelligibility and esthetic value of sounds. However, the benefits are variable between patients (Gantz et al., *Laryngoscope* 2005; 115:796-802). This raises the issue of how electric and acoustic stimulation interact in the cochlea.

In this study the effects of ipsilateral electric stimuli on acoustically evoked cochlear potentials were examined using a forward masking paradigm in guinea pigs. After exposure of the cochlea in anaesthetised animals, extracochlear stimulation electrodes were placed on the round window and on, or near, the basal turn. Recording electrodes were placed on the apex of the cochlea and on the bulla wall. The acoustically evoked compound action potential (CAP) was measured in response to pure tone bursts from 0.5-16 kHz. Maskers were presented as a train of 10 biphasic, alternating pulses at 1 kHz. The effects of different masker-dependent parameters (current strength and masker-to-probe interval) and probe-dependent parameters (frequency and tone intensity) on CAP amplitude were examined.

Electric masking reversibly reduced the amplitude of acoustically evoked CAPs. Masking increased with higher electric current levels and shorter masker-to-probe intervals, and was more pronounced at high tone frequencies (8 and 16 kHz) of low acoustic levels. At high acoustic frequency and low acoustic level, the observed amount of masking could be as high as 90%, while CAP latency increased by no more than 0.2 ms. Masking of CAPs elicited by lower acoustic frequencies was less pronounced, probably due to the fact that the electric masker was presented basally on the cochlea.

The results support the idea that high frequency cochlear regions can be stimulated electrically without affecting low frequency hearing, either by limiting the use of apical electrodes in conventional implants, or by using short electrode arrays (Gantz and Turner, *Acta Otolaryngol* 2004).

This work was funded by the Heinsius-Houbolt Foundation, The Netherlands

KEY WORDS: Cochlear implant, compound action potential, electric-acoustic stimulation, forward masking, guinea pig

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TITLE**ATAXIN-1 ACCUMULATIONS IN SCA1 DO NOT RESEMBLE 'CLASSICAL' POLYGLUTAMINE AGGREGATES****AUTHOR**Hilde A.G. Krol**DEPARTMENT/INSTITUTE**

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ABSTRACT

Spinal cerebellar ataxia type 1 (SCA1) is one out of 9 polyglutamine expansion disorders caused by the expansion of the amino-acid glutamine in the disease related protein. In SCA1 there is an expansion of glutamines in the protein ataxin-1. The polyglutamine stretch must exceed 36 glutamines to cause neurodegeneration. The main characteristic of these polyglutamine (polyQ) disorders is the presence of intracellular accumulations of the mutated protein, also called aggregates or inclusion bodies. We have investigated the aggregation features of several polyglutamine expanded proteins in living cells and found that the aggregation of ataxin-1 is different from all other expanded proteins. Intracellular accumulations of ataxin-1 are formed by both wildtype (non-expanded) and mutated (polyQ-expanded) protein. The accumulations seem to have an organized morphology and are mobile structures that are SDS soluble which is in contrast with other polyQ expanded proteins like huntingtin or the androgen receptor. Kinetics of the polyQ-expanded ataxin-1 are even enhanced when compared to wild-type ataxin-1, and nuclear export is not affected (which is in contrast to popular belief). As the polyQ-expansion doesn't lead to aggregate formation, we are now examining the effects of polyQ expansion on ataxin-1 function in downstream processes.

KEY WORDS: Polyglutamine disorders, neurodegeneration, SCA1, aggregation**TELEPHONE-NUMBER:** 020-5664974**E-MAIL-ADDRESS:** h.a.krol@amc.uva.nl

TITLE**THE TRANSCRIPTION FACTOR NFIL3 IS AN INTRINSIC REGULATOR OF SUCCESSFUL NEURONAL REGENERATION****AUTHORS**

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ABSTRACT

Axons in the central nervous system (CNS) do not regenerate after injury, while injured axons in the peripheral nervous system (PNS) can regenerate successfully. One major limitation in successful regeneration in the CNS is the lack of intrinsic ability of neurons to express growth-promoting genes. In a previous study, gene-expression was monitored in dorsal root ganglions (DRGs) using microarray analysis, after either sciatic nerve (peripheral) or dorsal root (central) crush. One of the early-regulated genes that is specifically upregulated during successful regeneration is the transcription factor NFIL3.

Functional studies show that overexpression of NFIL3 induces neurite outgrowth in the F11 DRG neuroblastoma cell line. Unexpectedly, we find an even more pronounced induction of neurite outgrowth after knockdown of NFIL3. Together, these data led us to hypothesize that NFIL3 is an important regulator of neurite outgrowth. Our present study now aims to identify the downstream gene program of NFIL3. Using chromatin immunoprecipitation (ChIP) we can test the interaction of NFIL3 with promoter regions of candidate genes, predicted to contain NFIL3 consensus binding sites by bioinformatics approaches. We find a specific interaction of NFIL3 with the promoter regions of regeneration-associated genes such as *Atf3*, *Arginase 1* and *Gap43*.

In conclusion, we show that NFIL3 regulates a gene program involved in neurite outgrowth. These observations will be expanded by genome-wide analyses using ChIP combined with microarray technology (ChIP-no-chip). In this way, we will gain insight in the molecular mechanism of NFIL3 action in neuronal regeneration, providing a firm basis for future therapeutic approaches in neuronal injury.

KEY WORDS: Neuronal regeneration, gene expression, transcription factor, chromatin immunoprecipitation

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TITLE**NEUROTROPHIC TREATMENT OF THE AUDITORY NERVE IN DEAFENED GUINEA PIGS****AUTHORS)**

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ABSTRACT

One of the factors explaining the variability in perceptual performance of cochlear implant users is the degeneration of spiral ganglion cells (SGCs) in relation to extent and duration of sensorineural hearing loss. Several animal studies indicate that application of neurotrophic factors can enhance SGC survival and sensitivity to electrical stimuli. A significant SGC loss is observed in deafened guinea pigs which have been deaf for two weeks. When neurotrophic treatment started after degeneration had set in, the remaining SGC could still be rescued. Remarkably, Gillespie et al.¹ demonstrated that the protective effect was annihilated within two weeks after cessation of treatment.

Structure and function of SGCs were investigated in deafened guinea pigs treated with brain-derived neurotrophic factor (BDNF). Auditory brainstem responses (ABR) were recorded to confirm normal hearing. Subsequently, they were deafened by a co-administration of kanamycin and furosemide. Two weeks after deafening, the right cochleas were implanted with an electrode and cannula. The cannula was attached to a mini-osmotic pump (flow rate: 0.25 μ l/h) filled with brain-derived neurotrophic factor (BDNF; 100 μ g/ml). BDNF was administered to the cochlea for four weeks. Electrically evoked ABRs (eABRs) were recorded regularly. Electrical stimuli were monophasic pulses of 50-400 μ A and 20 μ s. The animals were sacrificed for histology, either immediately or two weeks after cessation of treatment.

Enhanced survival of SGCs has been found in the BDNF treated cochleas, even two weeks after cessation of treatment. This is in contrast with the data of Gillespie et al.¹. The eABR amplitudes remained higher in treated than in untreated deaf animals and were comparable to amplitudes in normal-hearing animals.

The effect of BDNF treatment to maintain SGCs in a viable condition lasts after cessation of treatment and, therefore, offers opportunity for therapeutic application.

This work was funded by the Heinsius-Houbolt Foundation, The Netherlands.

Reference

¹Gillespie L.N., Clark G.M., Bartlett P.F. & Marzella P.L. (2003) BDNF-induced survival of auditory neurons in vivo: Cessation of treatment leads to accelerated loss of survival effects. *J. Neurosci. Res.* 71, 785-790.

KEY WORDS: Cochlear implant, spiral ganglion cells, BDNF

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TITLE**THE ROLE OF SUMOYLATION OF DJ-1 IN PARKINSON'S DISEASE****AUTHORS**

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ABSTRACT

Parkinson's disease (PD) is a progressive age-related disorder characterized by the selective loss of midbrain dopaminergic neurons. Mutations in *DJ-1* gene, originally found by our group, have been linked to autosomal-recessive early-onset Parkinsonism in two European families. The DJ-1 wild-type (WT), but not the L166P mutant protein, has been shown to protect cells against oxidative stress. However the molecular mechanism that underlies DJ-1 action is yet to be fully understood. Aiming to gain insight in this direction we performed a yeast two-hybrid screening using DJ-1 as bait to identify proteins expressed in human brain that interact with DJ-1. Among known interactors, we found a group of components of the SUMOylation system: the E2 SUMO conjugating enzyme (UBE2I) and the E3 SUMO ligase (PIASx□), which suggests that DJ-1 is SUMOylated and/or regulates SUMOylation of other proteins. SUMOylation is a post-translational modification system that involves the covalent attachment of SUMO (Small Ubiquitin-related MOdifier) to lysine residues of substrate proteins with crucial roles in many different biological processes, including: protein localization, stability and regulation of gene expression. We have used the bimolecular fluorescence complementation strategy to visualize DJ-1/SUMO-1 conjugates in HEK293T and M17 neuroblastoma cells. Confocal imaging revealed that sumoylated DJ-1 is localized in a speckled manner in specific subnuclear structures. Additionally, we observed that SUMOylation of the DJ-1 L166P and M26I pathogenic mutants was decreased in comparison to WT, suggesting that sumoylation of DJ-1 may play a role in the neurodegenerative process. We are currently investigating whether DJ-1 SUMOylation is involved in the mechanism through which DJ-1 exerts its cytoprotective effect by examining the interaction in cells under stress conditions. Together the results of these experiments may help us to elucidate the pathway for DJ-1 modification, regulation of DJ-1 function and more importantly to determine how SUMOylation of DJ-1 may contribute to PD pathogenesis.

KEY WORDS: Parkinson's disease, DJ-1, SUMO-1, SUMOylation

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TITLE**HERITABILITY OF OBSESSIVE-COMPULSIVE SYMPTOMS****AUTHORS**

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ABSTRACT

Historically, family-genetic studies have strongly suggested genetic factors to be important in the development of obsessive-compulsive disorder (OCD). For the determination of the relative importance of genetic and environmental factors, twin studies are an obvious choice. Twin studies of OCD have a long history, starting back in 1929 and evolving from single case reports to large epidemiological studies. Within the Dutch twin register, several twin studies have been conducted on Obsessive-Compulsive (OC) symptoms. It was found that 55% of the differences of OC symptoms between children can be explained by genetic factors. Individual-specific environment explained 45% of the variation in OC symptoms. For adults, the heritability of liability to OC symptoms was 47% for both men and women. Familial resemblance was the same for DZ twins and non-twin siblings, which means that there was no evidence for a special twin environment. The remaining variance in liability was due to individual-specific environment. The same genetic risk factors for OC behavior were expressed in men and women. Lastly, we studied a population sample of female twins from the Virginia Twin Registry. After factor analysis, three reliable OC symptom dimensions were retained: Rumination, Contamination, and Checking. These OC dimensions were analyzed with multivariate genetic models to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions. The results suggest that a broad OC behavioral phenotype exists, influenced by both genes and individual-specific environment. In addition, we found evidence for specific genetic and environmental factors underlying the Contamination dimension.

KEY-WORDS: OCD, obsessive-compulsive disorder, OC symptoms, genetics, heritability, twin study

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TITLE**ADOLESCENT NICOTINE EXPOSURE IMPAIRS COGNITIVE PERFORMANCE DURING ADULTHOOD****AUTHORS**

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ABSTRACT

Adolescence is a developmental period, during which the brain and particularly prefrontal cortical regions thereof have not fully matured. Functionally, these regions play important roles in cognitive processes, such as behavioral inhibition and impulse control. Moreover, adolescents as a group are more likely to engage in the use of 'socially accepted' drugs, such as cigarettes. In this respect, epidemiological data have suggested that adolescent nicotine use may result in disturbances in cognitive function in adulthood.

In this study, male Wistar rats were pretreated with either nicotine (3 times daily, 0.4 mg/kg s.c.) or saline for ten days during (PND34-43) or following (PND60-69) adolescence. Five weeks later during adulthood, separate groups of animals were tested in operant paradigms taxing attention and distinct measures of impulsivity. Inhibitory control was tested in the 5-choice serial reaction time task (5-CSRTT), whereas impulsive choice was assessed in the delayed reward paradigm.

Our data show that adolescent, and not adult, nicotine exposure affects cognitive performance in adulthood and results in diminished attentional performance and increments in impulsive action. However, there are no differences in impulsive choice. Neurochemical analyses show increased dopamine reactivity in the mPFC of animals treated with nicotine during, but not following adolescence.

Taken together, these data show cognitive impairments caused by adolescent nicotine exposure. This suggests that tobacco use during adolescence may be a risk factor for disturbances in cognitive function later in life.

KEY WORDS: Adolescence, nicotine, cognition, attention, impulsivity

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TITLE**NEURONS IN THE FUSIFORM GYRUS ARE FEWER AND SMALLER IN AUTISM****AUTHORS**

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ABSTRACT

Abnormalities in face perception may be a core feature of social disabilities in autism. Recent functional magnetic resonance imaging studies showed that patients with autism can perform face perception tasks. However, the fusiform gyrus and other cortical regions supporting face processing in controls are inactive in patients with autism. The neurobiological basis of this phenomenon is unknown. We tested the hypothesis that the fusiform gyrus shows specific alterations in neuron density, total neuron number and mean perikaryal volume in autism. Using high-precision design-based stereology we investigated the fusiform gyrus (analyzing layers II, III, IV, V and VI separately) in 7 postmortem brains from patients with autism and 10 controls for volume, neuron density, total neuron number and mean perikaryal volume. To determine the specificity of the results the same analyses were also performed in the primary visual cortex and in the whole cortical gray matter. Data from patients with autism were compared to matching data from controls using a general linear model multivariate analysis of variance, with diagnosis as fixed factor and gender, age, hemisphere, brain weight, postmortem interval and fixation time as covariates. Compared to controls, patients with autism showed significant reductions in neuron densities in layer III (-13.1%), total neuron numbers in layers III (-23.7%), V (-14.3%) and VI (-10.6%), respectively, and mean perikaryal volumes of neurons in layers V (-21.1%) and VI (-13.4%), respectively, in the fusiform gyrus. None of these alterations were found in the primary visual cortex or in the whole cerebral cortex. The results of the present study may provide important insight about the cellular basis of abnormalities in face perception in autism.

KEY WORDS: Autism, face processing, fusiform gyrus, design-based stereology

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TITLE**GENETIC DISSECTION OF MOUSE ANXIETY-RELATED BEHAVIOR****AUTHORS**

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ABSTRACT

The modified hole board (mHB), which is a complex behavioral test for rodents, allows us to assess for a variety of different motivational systems in parallel (i.e. exploration, locomotion, avoidance, arousal, memory, and risk assessment). This approach is essential for behavioral characterization since the motivational system of interest is strongly influenced by other behavioral systems. In previous experiments the C57BL/6J and A/J mouse inbred strains were behaviorally phenotyped in the mHB and showed differences in almost all motivational systems. To elucidate the genetic mechanisms underlying those behavioral differences, we performed further analyses with a commercially available set of mouse chromosome substitution (CS) strains. For this set C57BL/6J is the host strain and A/J is the donor strain. We identified one CS-strain (C57BL/6J-Chr19^A/NaJ) that differed in avoidance behavior (i.e. anxiety) from the C57BL/6J, but not in locomotion. Thus pleiotropic contribution of locomotion could be excluded. To identify which of the genomic regions that the CS-strain inherited from the A/J are responsible for this phenotype, an F₂-intercross between C57BL/6J and the CS-strain is currently produced. After quantitative trait loci analyses we hope to identify candidate genes and future work will be directed towards use of knockout strategies and micro-array analyses to assess the contribution of these candidate genes in relation to anxiety-related behavior.

KEY WORDS: anxiety, mouse chromosome substitution strain, genetics, QTL

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TITLE

SYNTHESIS OF ^{18}F -LABELLED CUBYL-WAY

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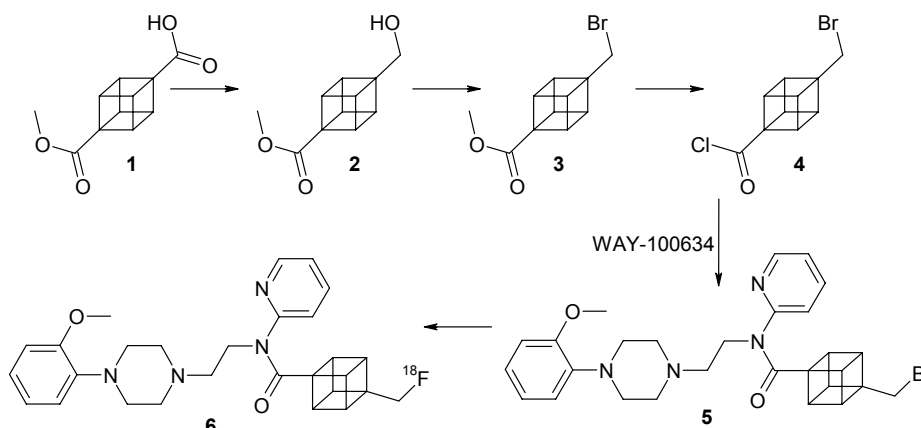
ABSTRACT

Introduction

Earlier we have found that substitution of the cyclohexyl group in WAY-100635 by a cubyl moiety does not really alter the affinity for the $\text{HT}_{1\text{A}}$ -receptor. Furthermore we have shown that [^{123}I]iodocubyl-WAY binds to this receptor in rat brain. Since we have recently found that the hydrolysis rate of this compound when incubated with human hepatocytes is much lower than for e.g. MPPF, we decided to prepare an analogous fluorine-18 labelled derivative. Although direct substitution of a bridgehead iodine with [^{18}F]XeF $_2$ is possible, this would lead to a compound with low specific activity. Therefore we have introduced a $-\text{CH}_2^{18}\text{F}$ function on the bridgehead for which elimination of HF is also impossible.

Results

Reduction of **1** with $\text{BH}_3 \cdot \text{SMe}_2$ in dry THF under argon gave **2** in 70 % yield. Further bromination with $\text{CBr}_4/\text{triphenylphosphine}$ in THF under argon gave **3** in 80 % yield. The ester was then saponified with NaOH and subsequently treated with SOCl_2 in dry MeCN, to give the acid chloride **4** in 60 % yield. WAY 100634 and TEA in MeCN were added to **4**, to give **5** in 90 % yield.



Radiofluorination of **5** with ^{18}F in dry MeCN using kryptofix and K_2CO_3 gave **6** in a labelling yield of 80% in ten minutes. Separation from the precursor is easily performed using reversed phase HPLC yielding a chemically and radiochemically pure product.

Results and Discussion

The ease of which the nucleophilic labelling occurs is surprisingly. Probably this is due to the fact that the exocyclic carbon-carbon bond has a higher degree of S -character than in normal aliphatic bromides. Compound **6** was further found to be thermally stable on heating for 60 minutes at 130°C in acetonitrile in a closed vial, in contrast to its precursor **5** which has to be stored in a refrigerator. The stability of **6** towards serum or hepatocytes is still not known.

Conclusion

A simple high- yield synthesis for a nca ^{18}F - labelled analogue of WAY-100635 has been developed. Affinity and selectivity of this compound *in vitro* as well as *in vivo* is now under investigation.

KEY WORDS: WAY-100635, cubane, 5-HT $_{1\text{A}}$, fluorination

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TITLE**DO PITX3 AND EN1 INTERACT IN THE MESODIENCEPHALIC DOPAMINERGIC (mdDA) SYSTEM?****AUTHOR**Maria Alves dos Santos**DEPARTMENT/INSTITUTE**

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ABSTRACT

The mesodiencephalic dopaminergic (mdDA) system is involved in the control of movement and behavior. These neurons are located in three distinct nuclei in the midbrain, one of which is the substantia nigra pars compacta (SN). The loss of dopaminergic neurons in this neuronal population is the neuropathological hallmark of Parkinson's disease (PD). The homeobox transcription factors engrailed 1 (En1) and Pitx3 are expressed in the SN from early in development to adulthood (the expression pattern of these genes in the brain is restricted to the mdDA system). It has been shown that the *En1* participates directly in the regulation of mdDA apoptosis, a proposed mechanism for Parkinson's disease. Indeed, the deletion of the two *En1* leads to the prenatal loss of DA neurons in the SN, via apoptosis. Furthermore, the (*En1*^{+/-};*En2*^{-/-}) mice adult phenotype resembles key pathological features of PD – progressive degeneration of dopaminergic neurons restricted to the SN of young adult mice, motor deficits similar to akinesia and bradykinesia, and a lower body weight. This phenotype shares molecular similarities with the *Aphakia* mutant, the Pitx3 mouse mutant. This raises the question whether these two genes interact functionally in the molecular developmental program of the mdDA system as well as in its adult physiology.

The practical goals for the coming time are to find the downstream targets and interactors of these genes, focusing on their role in the survival of the SN mdDA neurons. This will be followed by both analyses *in vitro* and *in vivo* of the genes found.

The general aim, with a wider time scope, is to better understand mdDA development, maintenance and function, thereby enhancing the possibilities for clinical intervention in human mdDA pathology.

KEY WORDS: Pitx3, En1, mesodiencephalic dopaminergic (mdDA) system, mdDA development, Parkinson's disease (PD), apoptosis

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TITLE**DETERMINATION OF OPTIMAL ADENO-ASSOCIATED VIRAL VECTOR SEROTYPES FOR TRANSGENESIS IN THE LATERAL HYPOTHALAMUS OF THE RAT****AUTHORS**Marijke W.A. de Backer, M. Luijendijk, M. Brans, K. Garner, R.A.H. Adan**DEPARTMENT/INSTITUTE**

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ABSTRACT Until now, recombinant adeno-associated virus serotype 2 (rAAV2) vectors were the mostly used serotypes of AAV for the overexpression or knock down of genes in many tissues. Recently new serotypes were discovered which resulted in different transduction patterns than rAAV2. This difference in transduction patterns is due to the fact that the different serotypes use different receptors and/or pathways to transduce cells. So far, these new serotypes were tested in the central nervous system in "hot" brain regions like striatum and hippocampus, were they transduced much more cells. For our research we are interested to genetically interfere with signalling in the hypothalamus. However transduction patterns of other serotypes than rAAV2 are not investigated in this brain region.

We hypothesized that other serotypes might be better capable to transduce neurons of the lateral hypothalamus.

To investigate this hypothesis we compared the transduction patterns of rAAV 1, 2 and 8 and combined coats 1/2, 2/5 and 2/8 in vitro and in vivo.

Injection of serotype 1 in the lateral hypothalamus of the rat transduced the most cells and resulted in the largest transduction area compared to the other serotypes. These results will be used to encapsidate rAAV vectors containing shRNA's/ genes which are involved in energy balance. This in order to be able to dissect the roles of different brain regions and neural pathways involved in energy balance.

KEY WORDS: AAV, serotypes, lateral hypothalamus, rat

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TITLE**GFAP-DELTA EXPRESSION IN SUBVENTRICULAR ZONE ASTROCYTES****AUTHORS**

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ABSTRACT

Subventricular zone (SVZ) astrocytes are a principal source of neural progenitors in the adult mammalian brain. In the rodent brain this region continuously generates new neurons for the olfactory bulb. It has also been shown that human astrocytes from the SVZ area, that form a ribbon lining the ventricles, divide *in vivo* and produce multipotent self-renewing neurospheres *in vitro*. In our group, we have identified an astrocytic protein, GFAP- δ , which is mainly expressed in neurogenic regions, such as the SVZ, and is thus a potential marker for neural progenitors.

Our aim is to study the population of GFAP- δ positive SVZ astrocytes to determine whether these astrocytes are indeed neural progenitors. Also, we intend to use GFAP- δ as a tool to study the SVZ astrocytes in Parkinson's disease, as it has been shown that dopamine depletion of the striatum, such as in Parkinson's disease, may lead to a decrease in neurogenesis.

Currently, we are investigating expression of GFAP- δ throughout the subventricular zone using immunocytochemistry. Double-labeling with various proliferation markers will show whether the GFAP- δ positive cells are indeed neural progenitors. Further co-labeling studies will show the precise identity of the GFAP- δ positive cells. We will also study the expression of GFAP- δ specifically in the caudate nucleus of incidental and staged sporadic Parkinson patients and of age- and sex-matched controls, to see if we can replicate the decrease in neurogenesis which was found previously.

We have also developed neurosphere culture systems from both mouse and human subventricular zone, to examine GFAP- δ expression in stem cells in culture, and the expression pattern during proliferation, differentiation, and in Parkinson's disease.

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KEY WORDS: Neurogenesis, astrocytes, GFAP, Parkinson's disease

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TITLE

DETECTION OF LOW-LEVEL SOMATIC AND GERMLINE MOSAICISM BY DENATURING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY IN A EURO-MRX FAMILY WITH SLC6A8 DEFICIENCY

AUTHORS

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ABSTRACT

Creatine transporter deficiency is an X-linked mental retardation disorder, caused by mutations in the creatine transporter gene, *SLC6A8*. In a European Mental Retardation Consortium panel of 66 patients, we identified a male with mental retardation, caused by a c.1059_1061delCTT; p.Phe354del mutation in the *SLC6A8* gene. With the use of direct DNA sequencing, the mutation was also found in the brother of the proband, but not in their mother. However, by analyzing EDTA blood of the mother with denaturing high performance liquid chromatography (DHPLC), we could show that the mother displays low-level somatic mosaicism for the three base-pair deletion. This study indicates DHPLC as an important tool in the detection of low-level mosaicism, as does it illustrates the importance of considering somatic and germline mosaicism in the case of apparent *de novo* mutations.

KEY WORDS: SLC6A8, DHPLC, somatic mosaicism

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TITLE**MOLECULAR PATHOGENESIS OF TUBEROUS SCLEROSIS COMPLEX IN PATIENTS WITH INTRACTABLE EPILEPSY****AUTHORS**

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ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal dominant, multisystem disorder caused by mutations in either the *TSC1* or *TSC2* genes and is clinically characterized by several neurological manifestations including intractable epilepsy. The recent identification of activation of the mTOR pathway in TSC-associated lesions has contributed to our understanding of the molecular pathogenesis of TSC. However, the mechanism of cortical tuber formation is still under debate.

We will discuss the neuropathological characteristics of TSC and we currently use single-cell Laser Capture Microdissection (LCM) to investigate whether loss of heterozygosity (LOH) at the *TSC1* or *TSC2* locus is the underlying pathogenetic mechanism for cortical tuber formation.

The cortical tubers demonstrated disruption of the cortical lamination, together with the presence of abnormal cell types including dysplastic neurons and large bizarre neuroglial cells (giant cells). Immunohistochemically we confirmed the activation of the mTOR pathway, showing phosphorylation of the downstream effector ribosomal protein S6 in these abnormal cell types. DNA isolated from these cells expressing phosphorylated S6 is examined to determine LOH at the *TSC1* or *TSC2* locus. Normal appearing neurons and neurons in the perituberal cortex did not show phosphorylation of S6.

Up to now we could not confirm LOH as the underlying pathogenetic mechanism for cortical tuber formation, but more patients will be tested.

KEY WORDS: Tuberous sclerosis complex, intractable epilepsy, mTOR pathway, LCM, molecular pathogenesis

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TITLE**TOWARDS NEURAL CODING OF ATTENTIONAL PROCESSES IN MOUSE PREFRONTAL CORTEX****AUTHORS**

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ABSTRACT

Primate (including human) prefrontal cortex is concerned with many complex cognitive functions which are often described as 'executive'. For example, dorsolateral prefrontal cortex is thought to be involved in working memory, decision-making, reasoning, temporal organization of behaviour, and attentional control. Likewise, the rodent medial prefrontal cortex (mPFC) is critically involved in the guidance of behaviour. It governs functions like spatial working memory and movement planning. Furthermore, the mPFC has been implicated in attentional functions such as detection of stimulus features, attentional set-shifting and behavioural flexibility. Not much is known about the electrophysiological mechanisms underlying the involvement of the mPFC in attention. Therefore, we set out to investigate these mechanisms by recording neuronal activity in the prefrontal circuit, with special emphasis on the mPFC, in freely behaving mice. To this aim we designed a novel elongated 5-choice serial reaction time task (5-CSRTT)-box with an alley separating the reward side from the 5-choice area. Adult male C57BL/6 mice (> 28 grams) are trained to perform this operant five-choice test of attention after which mPFC unit activity and local EEG are recorded using a multiple tetrode driver (Neuralynx: 16 channels) linked to a Plexon data acquisition system. The training procedure consists of various stages. After completion of the task the mPFC is recorded in order to establish the neuronal representation of attention. Preliminary data recorded in the "5-lights phase" (respond to either of the 5 cuelights to gain a pellet) revealed event-related activity, such as inhibition of firing after reward delivery. In addition, location-dependent firing was found. Elucidating neurophysiological substrates within the attentional circuitry might be of clinical relevance for inattentiveness in psychiatric conditions such as ADHD.

KEY WORDS: Attention, prefrontal circuit, mPFC, in-vivo recordings, operant five-choice task

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TITLE
CHARACTERISTICS OF THE C2 DOMAINS OF DOC2B

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ABSTRACT
C2 domains all have a similar fold, consisting of an eight-stranded antiparallel β sandwich that serves as a scaffold for variable surface loops. Upon calcium binding to the loop region, C2 domains are able to interact with the lipid membrane due to electrostatic interactions. Despite the high structural similarity between C2 domains, they are known to exist in a variety of proteins with divergent functions. Doc2 is a protein containing two C2 domains and was shown to have a high calcium affinity. However, the molecular details of the calcium and lipid binding properties of the C2 domains of Doc2 are unknown. We used isothermal titration calorimetry to study calcium binding and found that the high affinity calcium binding of Doc2B is dependent on the C2B domain. Furthermore, using a FRET-based lipid binding assay, we found that lipid binding of Doc2 is enhanced in the presence of PIP₂. Additionally, both C2 domains seem to be necessary for calcium dependent lipid binding, suggesting the C2 domains function synergistically in this process.

KEY WORDS: Doc2, C2 domains, PIP₂

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TITLE**WHAT MAKES PARENTS HAPPY AFTER HEMISPHERECTOMY OF THEIR CHILD?****AUTHORS**

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Abstract**Introduction**

After hemispherectomy, parents report a considerable positive change in their child which is difficult to describe and which is not reflected in developmental index scores.

Purpose

To understand the positive feelings of the parents.

Methods

From the total of 25 children who had been followed from before hemispherectomy till two years thereafter, we selected those children (n = 6, age range 0.6 – 5.6 years) of whom structured interviews [Dutch translation of the Vineland Adaptive Behavior Scales (VABS)] were available. We also recorded seizure outcome (Engel classification).

Results

Developmental index scores did not change. Scores on receptive and expressive communication as well as on social relations improved when compared to pre-operative values particularly in children who had no post-surgical seizures.

Discussion

Parents' happy reports of positive change after hemispherectomy was not related to improvement of psychomotor function. Rather, it originated in their children's ability to actively participate in communication once seizures had disappeared or diminished.

KEY WORDS: Hemispherectomy, child, development, communication

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TITLE**A COMPARISON OF THE VESTIBULOTOXIC EFFECTS OF GENTAMICIN AND CO-ADMINISTRATION OF KANAMYCIN AND FUROSEMIDE IN GUINEA PIGS****AUTHORS**

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ABSTRACT**Objective**

The aim of our study was to investigate the immediate effect of co-administration of kanamycin and furosemide upon the vestibular system and to compare it to the vestibulotoxic effect of chronic gentamicin administration.

Material and method

Fifteen albino guinea pigs were used in this study. Five animals were injected with a single dose of both kanamycin (400 mg/kg, im) and furosemide (100 mg/kg, iv), 5 animals received daily gentamicin injections (100 mg/kg/day, ip) for 10 consecutive days, and 5 untreated animals served as a control group. Cochlear function was assessed by recording auditory brainstem responses (ABR) and vestibular function by measuring vestibular short-latency evoked potentials (VsEP).

Results

There was no effect of gentamicin upon cochlear function: ABR thresholds in the gentamicin group were comparable to those in the normal group. Combined kanamycin and furosemide administration resulted in a severe hearing loss (60 dB). There was a significant effect of gentamicin on vestibular function: VsEP thresholds were elevated and VsEP amplitudes showed a decrease. Co-administration of kanamycin and furosemide had no significant effect on the VsEP.

Conclusion

Kanamycin/furosemide co-administration as applied here has mainly a cochleotoxic effect, whereas chronic gentamicin administration has a vestibulotoxic effect.

KEY WORDS: Vestibular system, regeneration, ototoxicity, vestibular short latency evoked potentials (VsEPs)

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TITLE**THE ROLE OF NEUROTRANSMITTER SECRETION DURING AXON OUTGROWTH ON GROWTH CONE DYNAMICS****AUTHORS**Jurjen H.P. Broeke , M. Roelandse, M. Verhage**DEPARTMENT/INSTITUTE**

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ABSTRACT

Directed axonal outgrowth is important during brain development and secretion may play an important role in this process. Using silent mutants (munc13-1/2 double knockout and munc18-1 null), we investigated the role of secretion on growth cone dynamics such as outgrowth speed, accumulated distance travelled, the number of filopodia and their length as well as the growth cone area and motility. Work in dissociated cultures of controls and silent mutants has shown that outgrowth is decreased and motility is increased in silent neurons. When AMPA is added at 3DIV to wild type neurons, the outgrowth is increased, but not in silent neurons. In organotypic slice cultures of both silent mutants at 3DIV using time lapse imaging we found that AMPA increased the speed of directed outgrowth in WT but not in silent mutants. The results suggest that secretion regulates directed outgrowth through a presynaptic autocrine feedback loop.

KEY WORDS: Axonal outgrowth, growth cone motility, secretion, organotypic cultures, Munc13, Munc18**TELEPHONE-NUMBER:** 020-5986929**E-MAIL-ADDRESS:** jurjen.broeke@cncr.vu.nl

TITLE

SYNTHESIS AND EVALUATION OF [¹¹C]AF150(S), A POTENTIAL NEW AGONIST PET LIGAND FOR THE M1ACH-R

AUTHORS

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ABSTRACT

Introduction

The M1 muscarinic acetylcholine receptor (m1ACh-R) is the subtype with the highest density in the brain; they are concentrated in the basal ganglia, hippocampus, olfactory bulb and cortical areas. Lowest m1ACh-R density is found in the cerebellum. (1) It has been shown that M1 agonists can improve cognitive functions and modulate psychotic behaviour in patients with Alzheimer's disease and schizophrenia. (2,3) Moreover, animal data have shown that M1 agonists can revert amyloid plaque formation in Alzheimer's Disease. (4,5) To elucidate the function of the m1ACh-R in the aforementioned disease *in vivo*, a non-invasive molecular imaging technique could be of great benefit. One compound that is recognized as a potential tracer is AF150(S).

Aim

The synthesis [¹¹C]-AF150(S) and evaluation of the tracer in normal rats.

Experimental

[¹¹C]-AF150(S) was obtained by methylation of its desmethyl precursor AF400 through addition of [¹¹C]CH₃I to 1.0 mg AF400 dissolved in 500 µL MeCN. The product was purified by HPLC (Phenomenex Gemini 5µ C18 110A 10x250 mm; acetonitrile/water/DIPA 20/80/0.2, 6 mL/min) and extracted from the HPLC eluent by a Waters tC18 Seppak. Reformulation yielded [¹¹C]-AF150(S) in saline containing 7.09 mM NaH₂PO₄ and 20% ethanol. To determinate the *ex vivo* biodistribution, 16 rats received a bolus injection of 40 MBq [¹¹C]-AF150(S), in the tail vein, and were sacrificed at 5, 15, 30 and 60 minutes (N=4). Several tissues and distinct brain regions were dissected, weighed and counted for radioactivity.

Results

The incorporated yield of the [¹¹C]CH₃I is 74% (decay corrected) with a (radio)chemical purity of > 99%. First experiments show high brain uptake in the olfactory bulb, prefrontal cortex, cerebral cortex, basal ganglia and hippocampus with target to non-target tissue ratios of 1.83±0.07, 1.78±0.07, 1.38±0.06, 1.39±0.07 and 1.77±0.12 respectively at 30 minutes.

Conclusion

[¹¹C]-AF150(S) can be reproducibly synthesized in moderate yields. The tracer is rapidly cleared from the blood and shows good brain uptake. Regions known to be rich in m1ACh-receptors show higher uptake compared to regions devoid of m1ACh-receptors. Further studies are in progress to assess the properties of [¹¹C]-AF150(S) as a potential PET ligand.

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KEY WORDS: Muscarinic M1 receptor, agonist, brain, PET ligand

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TITLE**SCREENING FOR ASTROCYTE DERIVED SIGNALS INVOLVED IN NEURITE OUTGROWTH AND SYNAPTOGENESIS****AUTHORS**

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ABSTRACT

The development of the nervous system is a complex and highly regulated process and critical for the optimal performance of organisms. Alterations in neurite length and synapse formation and function correlate with cognitive deficits and mental retardation. Increasing evidence shows the importance of neuron-glia interactions during embryonic and adult neurogenesis as well as synaptic plasticity. Importantly, in the last decade, it has been shown that astrocyte-derived signals are necessary for neurite outgrowth and synaptogenesis. Some of the astrocyte-derived signals have been identified but the extensive elucidation of the astrocyte molecular pathways involved in neuronal development remains to be done. To approach this question in a large scale we are performing a high throughput screen, using small interference RNA (siRNA) to identify the astrocyte-expressed genes involved in this process. The siRNA is delivered to a monolayer of Astrocytes and mouse hippocampal neurons (E18) are cultured on top of it and maintained in serum-free conditioned media. Neurite outgrowth and synapse formation are monitored using the Cellomics KineticsScan HCS Reader. The KineticScan Reader is an automated inverted fluorescence microscope that is able to collect images from multi-well plates in a high-throughput manner and can be used as a first step in the functional identification of genes and pathways. The Kineticscan Reader collects fluorescent images (up to 6 channels) by scanning the entire surface of all wells of a 96-well plate in just several hours and without manual interference. An extensive set of highly flexible software tools can be used to analyze almost any cellular or subcellular process.

First we show that astrocytes support mouse hippocampal neurons (E18) survival at a density where neurons alone do not survive. Moreover, using immunostainings we found that neurite outgrowth and synaptogenesis are enhanced in the presence of astrocytes. Using our protocol, we found that more than 90% of the astrocytes, grown in monolayer, are transfected with siRNA. In line with this, we observed robust knock down for candidate genes studied so far, using Western blotting. The effect of siRNA mediated knock down in astrocytes on the outgrowth and synaptogenesis of cocultured neurons, for a selected group of genes, will be discussed.

KEY WORDS: Neuron-glia interaction, neurite outgrowth, synaptogenesis, high throughput screen, siRNA transfection

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TITLE**RATE-TO-PHASE TRANSFORM IN LAYER II PRINCIPAL NEURONS OF THE RAT MEDIAL ENTORRHINAL CORTEX****AUTHORS**

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ABSTRACT

The medial entorhinal cortex (MEC) and hippocampus are components of a brain network for spatial navigation. Hippocampal 'place cells' increase their firing rate when a rat is in a specific portion of an environment, their so-called 'place field'. Spatial navigation is also assisted by a temporal code, whereby each place cell fires at progressively earlier phases of the theta rhythm as a rat traverses through the place field of that cell, a phenomenon known as theta phase precession. Recently, it was reported that one synapse upstream of the hippocampus, MEC layer II principal neurons show phase precession, whereas layer III principal neurons do not (Hafting et al., SfN Abstr 2006), raising the possibility that phase precession arises between layers III and II of the MEC. We therefore asked whether increasing excitatory synaptic input from layer III neurons, which send their axons towards layer II, might be sufficient to drive phase precession in layer II neurons during theta oscillation. This question was addressed by dynamic clamp in anatomically-identified layer II principal neurons in acute slices from rat MEC (n=4). To mimic a natural conductance profile in layer II cells, we first used voltage clamp to measure the excitatory current evoked in layer II neurons by stimulation in layer III. Then we analyzed spike trains recorded from individual layer III neurons *in vivo*, to estimate the excitatory conductance profile seen by layer II cells during phase precession. Finally, dynamic clamp was used to play this conductance profile into layer II neurons *in vitro*, while mimicking theta oscillation by a rhythmic inhibitory conductance. We found that a simple rate-to-phase transform could produce 180 degrees of phase precession in layer II neurons, whereas further phase precession would require additional mechanisms, which are currently being investigated.

KEY WORDS: Entorhinal cortex, parahippocampal area, learning and memory, electrophysiology, phase-precession, phase-locking

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TITLE**IMPLICIT AND EXPLICIT EXPECTATIONS OF CANNABIS USE IN PATIENTS WITH SCHIZOPHRENIA AND RELATED DISORDERS****AUTHORS**

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ABSTRACT**Background**

Cannabis abuse has been found to be a component risk factor for the onset and poor outcome during the early course of schizophrenia and related disorders. Cannabis use has become a target for prevention and treatment of schizophrenia patients. To improve treatment for cannabis using schizophrenia patients, it is necessary to get more insight in their motivation and expectancies of cannabis use. In drug and alcohol research a distinction is made between *explicit* and *implicit* effect expectancies. *Explicit* expectancies can be measured by self-reports, and *implicit* expectancies can be measured by means of the implicit association test (IAT) which is a computer task. Implicit associations are measured to tap underlying cognitive-motivational processes that people are not aware of, and because they seem to be important predictors for substance use. Implicit expectations of cannabis use have never been tested in patients with schizophrenia before.

Aim of the study

To determine whether implicit expectancies of cannabis use are associated with personal drug use patterns, craving and explicit expectancies, and to determine whether the cannabis effect expectancies are different from those of people in the general population.

Method

Expectations of cannabis use are measured in male patients with schizophrenia and related disorders in the age of 16-30 years, and in male healthy controls who are matched for age and level of education. The aim is to assess 70 patients and 70 controls. *Explicit* expectancies are measured with the Marijuana Effect Expectancy Questionnaire and the Visual Analogue scale. *Implicit* expectancies are measured with an IAT, designed for this study. It is a categorisation task that measures reaction times. Furthermore, participants are interviewed about their lifetime and current drug use with use of the Composite International Diagnostic Interview, drug section. Craving for cannabis is measured with the Obsessive Compulsive Drug Use Scale (OC-DUS).

Results and conclusion

We are still in the process of including and testing patients and healthy controls, so at the congress I will show some preliminary results and give more details of the IAT used in this study.

KEY WORDS: Schizophrenia, cannabis, expectations, implicit, explicit

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TITLE**COMPARING AUDITORY VERBAL HALLUCINATIONS TO INNER SPEECH IN SCHIZOPHRENIA;
AN fMRI STUDY****AUTHORS**

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ABSTRACT**Objective**

Auditory verbal hallucinations (AVH) are a core feature of schizophrenia, but also occur in other disorders as in healthy subjects. Malfunction of the language system, more precisely the system underlying inner speech appears to be the most plausible cause of AVH. Exactly which deviation of the inner speech system leads to AVH is still elusive. In this study, we aimed to directly compare activation during inner speech to activation during AVH, in order to better understand the pathophysiology of AVH. However, hallucinatory activation cannot be obtained in a regular paradigm since it is a spontaneous ideosynchronic phenomenon.

Method

During scanning seventeen schizophrenia patients had to indicate the onset and end of their hallucinations. Subsequently all patients were scanned while silently generating words. Language regions activated in both conditions were identified through a group-wise conjunction analysis.

Results

The conjunction analysis showed activation of the bilateral inferior frontal gyrus, the right superior temporal gyrus and the left insula. Language regions activated specifically by the word generation task consisted of the bilateral dorsolateral prefrontal cortex, the supramarginal gyrus, the left superior temporal gyrus and the right anterior insula. The hallucination task exclusively activated the right posterior insula.

Conclusion

Since the major amount of language regions implicated in AVH were also active during the word generation task it is credible that AVH are a dysfunction of normal language. In contrary, the exclusive activation of the right posterior insula during hallucinations argues for a central role of this structure in AVH.

KEY WORDS: Auditory verbal hallucinations, inner speech, conjunction analysis, fMRI

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TITLE**THE SPHINGOLIPID RHEOSTAT INFLUENCES BRAIN ENDOTHELIAL INTEGRITY****AUTHORS**

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ABSTRACT

Sphingolipids are a class of membrane lipids that display structural diversity and complexity. Sphingolipids are enriched in specific membrane domains on the cell surface that play a role in cell-(immune)cell and cell-matrix interactions. Sphingolipid metabolism is mediated by a complex network of tightly regulated pathways which coordinate the production of bioactive lipids including sphingomyelin, sphingosine, sphingosine 1-phosphate (S1P), ceramide, and others. Ceramide and sphingosine are precursors of S1P but possess opposite functions. While S1P is associated with cellular survival and proliferation mediated by activation of its receptors S1P₁₋₅, ceramide and sphingosine are associated with cell growth arrest, stress responses and apoptosis. Sphingolipid metabolism is regulated by specific enzymes and can be induced by either stress factors, such as inflammatory mediators (ceramide and sphingosine producing enzymes), or growth and survival factors (S1P producing enzyme). The balance between ceramide / sphingosine and S1P is also referred to as the sphingolipid rheostat. Alterations in this balance may evoke a pro-inflammatory (ceramide) or anti-inflammatory responses (S1P), making this pathway an interesting target to modify inflammatory events. The immunosuppressant drug FTY720[®] (a sphingosine-1-phosphate receptor-1 agonist) is a compound known to interfere with the rheostat balance. Initial clinical studies suggest FTY720[®] can be successfully applied to treat multiple sclerosis (MS).

So far, it is unknown whether and how the rheostat balance is implicated in immune cell trafficking into the central nervous system, a critical event in MS lesion formation. We have investigated how alterations in the rheostat balance influence the function of the blood-brain barrier (BBB) and determine cellular migration using in vitro systems. Moreover, alterations in the ceramide contents in MS lesions will be discussed. Understanding the molecular mechanisms that regulate BBB functioning and integrity is crucial for identifying new targets that limit MS lesion formation and progression.

KEY WORDS: Blood-brain barrier, multiple sclerosis, neuro-immunology, rheostat

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TITLE**CONES PERFORM A NONLINEAR TRANSFORMATION ON A NATURAL TIME SERIES OF INTENSITIES****AUTHORS**

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ABSTRACT**Introduction**

Visual stimuli as encountered by animals in natural scenes are very different from random stimuli. They display strong correlations in space, time and wavelength, and often encompass a large range of intensities and contrasts. Much of the processing in the early stages of visual processing, in particular those in the retina, is concerned with reducing these correlations and compressing the intensity and contrast ranges such that they fit the limited dynamic range of neurons. Here we concentrate on the first step in visual processing, in cone photoreceptors of the vertebrate retina. We will look at how natural stimuli are processed by cones, and investigate if the critical physiological steps involved can be identified and understood using a biophysical model of the cone.

Materials and Methods

Whole cell current-clamp recordings were made from cones in the isolated goldfish retina. We first determined the dynamic properties of cones using sets of flash and sine wave stimuli of various contrasts. Next a natural time series of intensities (NTSI) recorded outdoors, was presented to analyze the processing strategy of cones. This stimulus has a high dynamic range, a wide temporal frequency bandwidth, and considerable temporal correlations. A biophysical model of the cone (van Hateren, 2005) was fitted to the resulting cone responses and the parameters were compared to those obtained for primates.

Results

Flashes and Sinusoids: Stimuli of identical contrasts yield increasing response amplitudes at increasing light intensity levels and the responses become faster. Responses to sine waves start to decrease in amplitude at frequencies of about 5 Hz. In addition, responses to sine waves become distorted at high contrasts. The cone model satisfactorily fits the data over the entire range of light intensities. The model shows that the sine wave distortions can be attributed to a nonlinearity caused by cGMP hydrolysis and to calcium feedback in the outer segment.

NTSI: The time series used shows an intensity distribution which is skewed towards the lower intensities and has a long tail into the higher intensity region. This kind of distribution is typical for different collected NTSIs. The voltage distribution of the response is quite symmetrical and thus transformed compared to that of the original stimulus. This shows that the cone devotes a large portion of its dynamic range to the low intensity part of the NTSI.

Conclusion

The model shows that response kinetics of goldfish cones are significantly slower than primate cones. Given a Q_{10} between 2 and 4 these differences may mainly be due to temperature differences between experiments, corresponding to species differences in body temperature. Although it is often assumed that the early steps in visual processing are essentially linear the collected responses can only be adequately described by a nonlinear cone model. The observed nonlinearities can be fully understood from what is known about the phototransduction system in cones.

KEY WORDS: Phototransduction, cones, natural stimuli, goldfish

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TITLE**VISUALISING INTRACELLULAR AGGREGATE FORMATION AND CLEARANCE USING NON-DEGRADABLE FLUORESCENT PROTEIN FRAGMENTS****AUTHORS**

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ABSTRACT

Protein aggregates are a recurring phenomenon in several neurodegenerative diseases, such as Alzheimer's disease and various polyglutamine disorders including Huntington's disease. Here, particular protein fragments (peptides) appear to be non-degradable by proteases/peptidases present in the cytosol, leading to accumulation and subsequent aggregation. Although the underlying mechanism of aggregate formation is poorly understood, it is thought that intermediate stages of aggregation are toxic to cells. To visualize and manipulate the aggregation process in living cells, we developed a peptide-based model mimicking the described intracellular aggregation process. Indeed, peptidase-resistant fluorescent peptides start to form cytoplasmic accumulations within hours upon introduction into living cells. The main advantage of this model is the usage of peptides instead of commonly used vector encoded protein models, as peptides can be chemically modified e.g. fluorescent groups and tags can be added and length, conformation and sequence can be varied. No expression of vector encoded proteins is required, allowing immediate visualization of aggregation processes in time as these accumulations are formed within a few hours upon introduction.

Similar to disease-related protein aggregates, the peptide accumulations travel in a microtubule dependent manner towards the peri-nuclear region of the cell, shuttled by yet unknown cellular proteins. Surprisingly, common heat shock proteins do not affect the process. Clearance of these accumulations is however delayed when the autophagic inhibitor 3-methyladenine is used. We want to identify proteins that associate during different stages in the aggregation and clearance process, and will determine their role in neurodegenerative diseases.

KEY WORDS: Protein aggregation, peptide-based aggregation model, life-cell imaging, neurodegenerative diseases

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TITLE**CALCIUM-DEPENDENT CROSS-LINKING OF PHOSPHOLIPID MEMBRANES BY SYNAPTOTAGMIN-1****AUTHORS**

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ABSTRACT

Synaptotagmin 1 is the major calcium sensor in neocortical synaptic transmission. It belongs to a family of proteins that possess tandem C2 domains (also known as C2AB) implicated in calcium-dependent phospholipid binding. Calcium-sensitive synaptotagmins are thought to confer calcium sensitivity to the fusion of secretory vesicles with target membranes. Brain synaptotagmin 1 plays an important role in coupling the calcium signal to the release of neurotransmitters in neurons and is strongly conserved in metazoan evolution.

We have employed confocal imaging and optical trapping to study membrane cross-linking by C2AB at micromolar calcium concentrations. Our findings suggest that synaptotagmin 1 tandem C2 domain structure is necessary for liposomal aggregation. Individual C2A or C2B domains are not capable of cross-linking liposomes. We also show that calcium-dependent membrane cross-linking is a conserved property of divergent calcium-sensitive synaptotagmin isoforms. The optical tweezers experiments have allowed a more individual approach, where few liposomes were confined in a small space of a laser trap, thus reducing the time necessary for their aggregation. Together the data suggest that synaptotagmins can participate in vesicle exocytosis by exerting a direct force between two opposing membranes.

KEY WORDS: Synaptotagmin exocytosis optical trapping

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TITLE**THE INFLUENCE OF MATERNAL CARE ON LONG-TERM POTENTIATION IN THE ADULT RAT DENTATE GYRUS****AUTHORS**

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ABSTRACT**Background**

In humans, adversity in early life has been associated with an increased risk for adult psychopathology, but a functional link has still to be found. To get more insight how environmental events in early life can alter limbic brain function we have measured activity in the CA1 area and dentate gyrus of adult rats receiving variable amounts of maternal care.

Thus, in rats, the amount of maternal care provided to the pups in the first few days postnatally varies within the population, following a normal distribution. In this model, early experience has already been found to alter hypothalamo-pituitary-adrenal function and glucocorticoid receptor expression levels in several brain regions.

Methods

We determined the amount of maternal care provided to the pups by scoring several maternal behaviors during the first week postpartum. This led to classifying about 4% (average – 1 SD) of all mothers in the population as Low caring mothers, and about 12% (average + 1 SD) as High caring mothers. The effect of corticosterone and noradrenaline application (either separately or at the same time) on long-term potentiation (LTP) in the dentate gyrus was studied in male Low and High offspring. Also, tissue of these animals was used for morphological analysis of the dendritic trees and dendritic spines in the dentate gyrus.

Results

Under basal conditions, LTP could be induced in High, but not in Low offspring. Application of either corticosterone or noradrenaline separately reverses this phenotype, whereas concurrent treatment with these hormones had no significant effect.

Preliminary morphological analysis showed that dendritic spine density was significantly increased in High compared to Low offspring.

Conclusions

We have demonstrated that maternal care, an important early life event, influences synaptic functioning in the adult dentate gyrus, as was previously found in the CA1 area. High and Low offspring exhibit different amounts of LTP under basal conditions and react differently to the presence of stress hormones, suggesting that they are differentially influenced by stressful situations in vivo as well. It will now be important to elucidate the mechanisms underlying this phenomenon.

KEY WORDS: Maternal care, stress, long-term potentiation, morphology

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TITLE

DIFFERENTIAL EFFECTS OF CANNABIS AND NICOTINE ON THE HUMAN REWARD SYSTEM

AUTHORS

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ABSTRACT

Introduction

Cannabis is one of the most widely used drugs in the world. The active component, THC, binds to cannabinoid (CB1-)receptors, thereby altering neuronal firing of, for example, dopaminergic neurons¹. Long-term use leads to downregulation of CB1-receptors, which might be responsible for its addictive potential¹. In humans, high densities of CB1-receptors are found in the reward system, especially the nucleus accumbens, making it a prime target for cannabis research.

In the current study, we used fMRI² and compared brain activity between cannabis users and non-users during reward anticipation to test the hypothesis that chronic cannabis use leads to an attenuated response to rewarding stimuli in the nucleus accumbens. As cannabis is often used with tobacco, smokers were included as controls.

Methods

Fourteen cannabis users (13 males, mean age 24±4.4, 4331±2873.2 joints lifetime) were compared to thirteen cannabis naive healthy controls (11 males, mean age 24±2.7) and fourteen smokers (13 males, mean age 25±4.5). All subjects abstained from cannabis and alcohol for at least 1 week before examination. To activate the reward system, we used a monetary reward task³. During this task, cues were presented indicating a potential reward (cue for 2 euro) or no reward (cue for 0 euro). Following the cue, a target stimulus was presented to which subjects had to respond as fast as possible. Task difficulty was adjusted individually to ensure equal numbers of reward and non-reward trials. The measure of performance was reaction time on targets. SPM2 was used to preprocess fMRI data. The regression matrix contained factors modelling a) anticipation of reward (i.e. response to reward cues), b) anticipation of no reward (i.e. response to neutral cues), c) response to target stimuli, and factors modelling feedback. Group activation maps were generated for each factor using MULTISTAT. The contrast of interest was a versus b. A whole-brain group analysis was performed to compare groups.

Results

Performance did not differ between groups. All subjects responded faster when anticipating reward. Compared to nonsmoking controls, cannabis users showed reduced reward activity in the nucleus accumbens and caudate nucleus bilaterally, the left putamen, several frontal areas and the left cingulate gyrus. When comparing users to the smokers control group, reduced reward activity was observed in the caudate bilaterally, the left putamen, the left thalamus, and frontal areas. This indicates that in these areas, reduced reward activity is not due to nicotine but specifically to cannabis.

Discussion

Cannabis users show attenuated reward activity in the nucleus accumbens when compared to nonsmoking controls, but not when compared to smoking controls, indicating that this attenuation is possibly a result from nicotine use rather than cannabis. In the caudate and left putamen activity was reduced compared to both control groups, suggesting a specific cannabis effect. This study supports that chronic cannabis use leads to a reduced response of subcortical regions to rewarding stimuli.

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KEY WORDS: fMRI, cannabis, nicotine reward system

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TITLE**SCREENING OF THE CHROMOSOME SUBSTITUTION STRAIN PANEL TO IDENTIFY FEBRILE SEIZURE SUSCEPTIBILITY GENES****AUTHORS**

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ABSTRACT

Febrile seizures (FS) are the most common seizure type in children affecting 2-5% of the population. FS occur in young children between the age of 6 months and five years. Complex FS are a risk factor in the development of temporal lobe epilepsy (TLE). Although, the mechanisms underlying FS are largely unknown, recent association, family and twin studies indicated that genetic background is important in FS. The aim of this study is to identify FS susceptibility genes and cascades using a panel of mouse chromosome substitution strains (CSS).

To this aim, we determined the sensitivity to FS in both genders for the host strain (C57, $n=40$), the donor strain (A/J, $n=9$) and each strain of the chromosome substitution panel ($n=9$). Therefore, complex FS were induced by exposing these mice to a hot-air stream of 50 °C for 900s at postnatal day 14. During this period mouse behavioral repertoire (Ethovisionth) and body temperature (temperature transponders) were continuously monitored. Preceding electro-encephalographic (EEG) recordings ($n=7$) indicated that the incidence of hyperthermia-induced clonic-tonic convulsions (status epilepticus, SE) was paralleled by typical EEG epileptical activity (spike-wave discharges). Therefore, SE latency, thus the most reliable behavioral phenotype characteristic for the expression of seizures, was chosen as parameter for FS sensitivity in the present study.

C57 mice (seizure latency 623.6s \pm 13.8 (mean \pm S.E.M.)) were more susceptible ($p < 0.001$) to hyperthermia than the A/J mice (seizure latency 858.2s \pm 17.7). Screening of the whole panel for seizure susceptibility resulted in five strains with seizure latencies that differed significantly from C57 ($p < 0.001$). Within these five strains, 1) no difference in seizure susceptibility was found between genders, 2) two strains showed the AJ phenotype, 3) two other strains were more susceptible to HT than C57. At present, QTLs are identified on each of the chromosomes by backcrossing these five strains.

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TITLE**HYDROCHLOROTHIAZIDE INDUCED TINNITUS: A CASE REPORT****AUTHORS**

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ABSTRACT

One of the possible causes of tinnitus is ototoxicity of drugs. Numerous drugs are known to be able to cause tinnitus, with or without accompanying hearing loss. This poster presents the case of a patient whose tinnitus was caused by the diuretic hydrochlorothiazide (HCT). The case illustrates the need for a thorough history in tinnitus patients. Because HCT was recognized as a potential cause, the patient was treated quickly, effectively and easily. This diagnosis was missed earlier, which could have resulted in the patient undergoing unnecessary surgery. This is the first case presenting HCT as a possible cause of tinnitus. The induction of tinnitus has not been reported for HCT yet, although diuretics (mostly loop diuretics) are a well known potential cause of tinnitus.

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TITLE**IDENTIFYING THE SPECIFIC ROLE OF TRANSCRIPTION FACTORS *LMX1A* AND *LMX1B* IN THE GENETIC CASCADE LEADING TO MDDA DEVELOPMENT****AUTHORS**

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ABSTRACT

Meso-diencephalic dopaminergic neurons (mdDA) are involved in the control of voluntary movements and the regulation of emotion-related behaviour, and selective degeneration of these neurons in the substantia nigra (Snc) causes various neurological and psychiatric disorders, like Parkinson's disease (PD), depression and schizophrenia. An until thus far not well specified genetic cascade controls the generation and maintenance of mdDA neurons, and characterization of this cascade may help in the engineering of mdDA neurons from stem cells, which eventually might lead to stem cell-based therapies for PD.

Among several of the already characterized transcription factors found to be involved in mdDA neuronal development, are the LIM homeodomain proteins *Lmx1a* and *Lmx1b*. LIM homeodomain proteins are transcriptional activators that cooperate with other activators to direct cellular differentiation. Both *Lmx1a* and *Lmx1b* are required to trigger differentiation into mdDA neurons, and are expressed in overlapping fields in DA cell progenitors, early in the molecular program leading to mdDA neurons. It is already known from previous studies, with *Lmx1b* knock-out mice, that lack of *Lmx1b* results in improper differentiation of mdDA neurons; the mice showed absence of Pitx3 expression in TH positive neurons, a factor that is required for proper specification of mdDA neurons. Together with this improper specification, an early loss of neurons was also found in the knock-out mice.

Despite the fact that *Lmx1a* and *Lmx1b* both are necessary for generation of mdDA neurons, these factors have different roles in mdDA development. *Lmx1b* can not compensate for *Lmx1a*, and from previous studies it became clear that *Lmx1a* is a more efficient inducer of mdDA neurons in embryonic stem cells (ES-cells). *Lmx1b* is, in contrast to *Lmx1a*, not restricted to mdDA progenitor cells at early developmental stages, but has a much broader expression field.

To investigate how these two factors are exactly involved in mdDA neuronal development and maintenance, we first have to identify the exact role of these transcription factors in the molecular cascade. Our aim, to elucidate the transcriptional profile of *Lmx1a* and *Lmx1b*, can be reached partially by identification of their indirect and direct targets through Micro Array and Chip on chip analysis, respectively.

KEY WORDS: Meso-diencephalic dopaminergic neurons, neuronal development, transcriptional profile, transcription factors *Lmx1a* and *Lmx1b*

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TITLE
WHEN REMEMBERING HINDERS LEARNING

AUTHORS

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ABSTRACT

According to current memory models, retrieval of memories requires reactivation of the same brain regions involved in the initial encoding of the memories. Yet, counter to this widely-accepted idea, recent fMRI studies suggest opposing levels of brain activity during encoding and retrieval. In particular, increased activity in posterior cingulate cortex (PCC) and lateral parietal (PLPC) cortex has been associated with successful memory retrieval, but decreased activity, with successful memory encoding. These findings suggest a potential competition in our memory system between learning new information and remembering old information. This study tested the hypothesis that remembering hinders learning when both processes happen concurrently. During scanning, participants intentionally remembered old words displayed in the foreground while incidentally learning new scenes displayed in the background. The study yielded three main findings. First, successful retrieval of old information was associated with impaired learning of new information. Second, this behavioral effect was coupled with suppression of learning-related brain activity. Third, activity in left mid-ventrolateral prefrontal cortex (mid-VLPFC) was negatively correlated with the suppression effect, suggesting that mid-VLPFC can resolve the memory competition by allowing rapid switching between learning and remembering.

KEY WORDS: Declarative memory • episodic memory • fMRI • prefrontal cortex

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ITILE**POTENTIAL ROLE OF THE IMMUNE SYSTEM IN HUMAN TEMPORAL LOBE EPILEPSY****AUTHORS**

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ABSTRACT

One of the most common forms of acquired epilepsy in adults is temporal lobe epilepsy (TLE). The predominant subtype of this syndrome is mesial temporal lobe epilepsy (MTLE), here the focus of epilepsy can be found in the mesial temporal structures; particularly the hippocampus. The onset of the disease is thought to occur due to an 'initial insult' such as complex febrile seizures, head trauma or brain infections. This initial insult is typically followed by a latent period where no seizure activity is seen yet. After this latent period TLE develops, often associated with rapid increases in duration and frequency of seizures, despite drug treatment. Approximately 25% of TLE patients become medicinally intractable.

Recent results from clinical and experimental studies have implicated components of the immune system in the etiology and progression of TLE. We have recently shown in a genome wide microarray analysis on hippocampal specimen from TLE patients, that chemokinegenes are strongly affected in MTLE patients.

Presently, we are investigating the role of chemokines and several signal transduction pathways. Two different juvenile rodent models for TLE are used in this research: the hyperthermia model (HT) for febrile seizures and the pilocarpine model for MTLE. The HT model is particularly useful for determining the susceptibility of an animal for febrile seizures and to analyse mild changes due to the initial insult, and the pilocarpine model is used to monitor the latent phase and the progression of MTLE. To study the chronic end-stage of MTLE, human hippocampal material obtained from hippocampal resections from patients suffering from intractable MTLE is used. By using these three biological systems we hope to gain more insight into the molecular changes in immunological processes that occur in MTLE brain tissues.

Epilepsy induced changes in the biological samples will be analysed by immunohistochemistry, western blotting, in situ hybridisation, microarrays and ELISA. The project has recently started. The preliminary findings of this study will be presented at the meeting.

Acknowledgements: This work is supported by the EPOCH foundation.

KEY WORDS: Temporal lobe epilepsy, hyperthermia, pilocarpine, immune system

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TITLE**BLOOD-BRAIN BARRIER CHARACTERISTICS IN MS LESIONS****AUTHORS**

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ABSTRACT

The blood-brain barrier (BBB) is a selective barrier between the central nervous system (CNS) and the systemic circulation and is essential for maintenance and regulation of the neuroparenchymal environment and optimal neuronal functioning. It acts as a physical barrier due to the presence of well-developed tight junctions between brain endothelial cells (ECs) that impede the entrance of circulating molecules and immune cells into the CNS. Specific transporter systems on the luminal and abluminal membranes regulate the transcellular traffic of small hydrophilic molecules. This makes the BBB a selective transport barrier, which permits the entry of essential nutrients (e.g. by glucose transporter 1, GLUT1) and excludes potentially harmful compounds (e.g. by members of the large family of ATP-binding cassette (ABC) transporters, such as P-glycoprotein, the multidrug resistance-associated proteins (MRP) and breast cancer resistance protein).

Loss of BBB integrity has been described in a variety of neuroinflammatory diseases, including multiple sclerosis (MS). It has been well described that during MS, leukocytes enter the CNS and form perivascular infiltrates. This is accompanied by enhanced BBB permeability. However, knowledge of transcellular barrier function towards small molecule transport during MS is lacking. Therefore, we examined the expression pattern of GLUT1 and different ABC transporters in various well-characterized MS lesions. Here we show that the expression of these transporters is increased in (chronic) active demyelinated MS lesions. In particular reactive hypertrophic astrocytes show high levels of these transporters, whereas on ECs the expression of MRP1 and 2 was downregulated in these lesions. Furthermore, we validated the expression profiles of the different transporters in vitro on human brain endothelial cells and primary human astrocytes. This work provides more insight into the transport barrier properties of the BBB during neuroinflammation, which may be of value for the development of novel delivery strategies to treat MS.

KEY WORDS: Multiple Sclerosis, blood-brain barrier, P-glycoprotein

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TITLE**THE EFFECTS OF ANTIPSYCHOTIC MEDICATION ON HIPPOCAMPAL VOLUME CHANGE IN SCHIZOPHRENIA****AUTHORS**

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ABSTRACT

Evidence suggests that schizophrenia patients show reductions in hippocampal volume relative to healthy subjects. However, it is unknown whether these are static or progressive over time and to what extent this volume (change) is confounded by the effects of antipsychotic medication. Two Magnetic Resonance Imaging brain scans were obtained with a mean interval of approximately 5 years of 95 schizophrenia patients and 113 healthy subjects (age-range: 16-58). The hippocampus was manually segmented. Patients and healthy subjects were matched for age, gender, parental education and scan interval.

Age-dependent volume change over time was compared between the groups. Furthermore, in patients the relationship between hippocampal volume change and cumulative medication intake was investigated.

Change over time did not differ significantly between the groups after correcting for age. However, healthy subjects showed a larger decrease in hippocampal volume with increasing age, while volume change in patients was stable over time, i.e. showing almost no change. Patients with higher doses of typical antipsychotics (haloperidol equivalents) showed larger hippocampal volume decrease over time ($n=52$; $\rho=-0.27$; $p=0.06$). In contrast, there was a positive relationship between cumulative intake of atypical antipsychotics (haloperidol equivalents; $n=49$; $\rho=0.31$; $p=0.03$), with olanzapine (milligram) showing a significant positive association with hippocampal volume change that reached trend level ($n=37$; $\rho=0.31$; $p=0.06$).

These findings suggest a different neurodevelopmental trajectory of hippocampal volume change in patients and healthy subjects. Interestingly, type and dose of antipsychotic medication intake appear important confounders and a possible neuroprotective effect of atypical antipsychotics, in particular olanzapine is suggested.

KEY WORDS: Antipsychotic medication, schizophrenia, hippocampus, longitudinal, MRI

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TITLE**PARKINSON DISEASE: FROM DYSREGULATED HUMAN BRAIN TARGETS TOWARDS NOVEL THERAPEUTICS****AUTHORS**

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disease. There is no clear understanding of its etiology and no effective treatment exists as yet. Although there are some theories on how the disease may start - such as oxidative stress, or aggregation of α -synuclein protein - there is still no clear insight into the pathogenesis of this disorder. Therapies used at present in the clinic for PD are symptomatic and do not halt the progression of the disease. In our research we follow-up the results of a microarray study performed on human post mortem tissue, where PD patients were compared to matched controls (Bossers *et al*, 2007- submitted) with the goal to find new molecular targets for developing a therapy for Parkinson's disease. The main aim of this TI Pharma project is to search for gene targets responsible for both the development of the disease as well as for its progression, which at the end can be easily targeted by specifically designed therapy. Currently we are selecting targets of interest and localizing their presence in human PD and control postmortem substantia nigra, obtained from the Netherlands Brain Bank, with the help of immunocytochemistry on the protein level, and *in situ* hybridization on the mRNA level. We have designed a relatively quick and high throughput method of protein detection with the use of multiple antibodies as well as an efficient RNA probe generation by the use of PCR amplification. The cellular and intracellular localization of these targets will help us in the design of *in vitro* studies where both large scale knockouts of the targets as well as specific cellular PD models will be used to further select and validate our genes of interest. Finally we will continue our work *in vivo* by use of genetic PD animal models. Our hope lies in finding a specific target with the capability of rescuing these animal PD phenotypes and validating the selected target as a possible candidate for future therapy.

KEY WORDS: Parkinson's disease, gene target identification, human postmortem tissue, target localization, new therapy development

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TITLE**12 HOURS OF FULL SLEEP DEPRIVATION BY MEANS OF FORCED LOCOMOTION DECREASES THE MOTIVATION FOR FOOD REWARD****AUTHORS**

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ABSTRACT**Introduction**

Operant tasks are often used to evaluate the effects of sleep deprivation (SD) on cognition. As performance is dependent on the motivation for food rewards, we investigated the interaction of SD and food restriction on operant behavior.

Methods

Male Wistar rats, kept on a diet of 16g rat chow/rat/day, were trained to a stable response level on a Fixed-Interval, Fixed-Ratio-task in which 3 lever presses within a 40s interval produced one reward pellet (maximum 64 rewards/session).

Subsequently, they were sleep deprived for 12h by forced locomotion during the light phase in a rotating sleep deprivation device. Rotational speed and alterations in direction were gradually increased during the deprivation period, reducing slow-wave-sleep to 1,4% of control days. The procedure was repeated two weeks later on a 14g/rat/day diet.

Data

Average numbers of lever presses in one session were 779 (SEM=130) and 1146 (SEM=170) on a diet of 16 and 14g/rat/day, respectively (average over 5 sessions, N=4). On average, rats obtained 60 and 62 pellets, respectively.

After 12h of total SD, total lever presses were decreased by 81% and 65% for 16 and 14 g/rat/day, respectively. The number of collected rewards after SD was reduced by 81% and 54% for 16 and 14g/rat/day, respectively.

Conclusion

Lever-pressing for food reward in a FI40FR3-task is dramatically decreased after 12h of SD by forced locomotion, suggesting that the motivation to perform a food-rewarded operant task is strongly affected. A more stringent food restriction scheme partially restores normal lever-pressing activity.

KEY WORDS: Sleep deprivation, operant behaviour, food restriction, motivation

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TITLE**CHARACTERIZING PINKY AND THE BRAIN: OPERANT LEARNING AS A TOOL FOR BEHAVIOURAL SCREENING AND QTL MAPPING OF RECOMBINANT INBRED MICE****AUTHORS**

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ABSTRACT

Our knowledge of the genome of humans and other mammalian species has been rapidly increasing, but relatively little is known yet about the functions of these genes in cognitive processes, such as learning and memory.

The aim of the project is to elucidate the relationships between chromosomal loci and heritable behavioural traits related to memory and learning processes by mapping quantitative trait loci (QTL's) that correlate with behavioural-cognitive abnormalities, leading to the identification of genes which play a role in memory and learning processes and corresponding cognitive disorders.

In order to find QTL's, a large number of recombinant inbred (BxD) mouse lines are screened for behavioural-cognitive abnormalities using appetitive conditioning paradigms. BxD mouse lines are the most extensive set of recombinant inbred strains available and their chromosomes have a high number of unique recombinations as well as identifiable molecular markers. Together, these properties provide a high chance of tight trait-marker linkages and allow QTL mapping with high resolution.

The first step of behavioural training is a classical conditioning task in which the mice have to learn to associate a stimulus light with a reinforcer. In the next stage, an operant conditioning task, the mice have to learn to press a lever in order to get a reinforcer.

According to the performance of the mouse lines tested so far (24 BxD mouse lines and 6 common inbred mouse lines including the parental lines, N=6-12 per line), the acquisition of operant behaviour has remarkable variation across the recombinant inbred mouse strains. The heritability estimate (cf. Isles et al, J.Neurosci., Jul 2004; 24: 6733-6740) for the operant performance was 19.2%, suggesting that the variability of performance between different mouse lines can partially be explained by genetic differences between the lines. To study the genetic component of operant task performance further, a preliminary QTL mapping was performed, resulting in suggestive QTL's that may contribute to the acquisition and performance of operant learning.

KEY WORDS: Quantitative genomics, mouse phenomics, phenotypical screening, complex trait analysis, QTL mapping, recombinant inbred mice, BxD, operant learning, appetitive conditioning

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TITLE
MEMORY AFTER TEMPORAL LOBECTOMY IN CHILDREN

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ABSTRACT

Aim

To explore individual variation in memory outcome after temporal lobectomy in children. Subjects: 49 consecutive patients who received temporal lobectomy for intractable epilepsy below the age of 18 years.

Methods

Retrospective review of neuropsychological files yielded 22 patients with pre- and post-surgical memory data (median age 15 years; range 8-17).

Results

Memory scores improved permanently in 8 patients and deteriorated in 5 patients. Four patients showed a temporary change in memory performance. Two patients showed no change and 3 patients had unclear or contradictory results. Five patients showed permanent improvement of verbal memory after right-sided lobectomy. Non-verbal memory showed both permanent improvement (3) and deterioration (3) after right-sided surgery, but mainly temporary deterioration (3) or stability (4) after left-sided surgery.

A prospective longitudinal study using a wide range of memory tests over the entire childhood age range is currently in progress.

KEY WORDS: Epilepsy, memory temporal lobe, children and adolescents

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TITLE

ELECTROPHYSIOLOGICAL BASIS OF FUNCTIONAL MRI SIGNALS IN RAT MODELS OF PERMANENT AND TRANSIENT CEREBRAL ISCHEMIA

AUTHORS

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ABSTRACT

Introduction

Functional MRI (fMRI) is increasingly applied as a neuroimaging tool to study changes in activation patterns after stroke. However, the electrophysiological basis of fMRI-detected changes in activation responses are unresolved. In this study we measured somatosensory evoked potentials (SEPs) in the forelimb region of the primary somatosensory cortex (S1fl) at different time-points after permanent and transient stroke in rats. Based on previous fMRI findings^{1,2}, we expected loss of SEPs in ipsilesional S1fl and increased contralesional electrical activity when the affected forelimb is stimulated acutely after stroke.

Methods

Experimental stroke was induced by permanent or transient (60-90 minutes) right middle cerebral artery occlusion (MCA-O) in male Wistar rats.³ SEP recordings were performed at 2 and 3 h (n=5) and at 24 h (n=3) after permanent MCA-O, and at 24 h after transient MCA-O (n=2). SEPs were simultaneously recorded epidurally from left and right S1fl with increasing and alternating electrical stimulation (0, 0.5, 1, 2, 4 and 8 mA) of the left and right forelimb under propofol anesthesia. After SEP recordings, animals were sacrificed for TTC staining of the brain to assess size and location of the ischemic lesion. SEP data were digitally low-pass filtered and analysis was done on the averaged SEP for each S1fl out of two sessions for each rat. We determined the Rate Dispersion Factor (RDF) for the 5-30ms latency range, which provides an index of the overall shape of the SEP waveform.⁴

Results

In all animals, normal SEPs were observed in contralesional S1fl when the unaffected forelimb was stimulated. At 2 and 3 h after permanent MCA-O, although reduced, significant SEPs were measured in right, ipsilesional S1fl when the left, affected forelimb was stimulated. At 24 h after stroke, ipsilesional SEPs were largely absent. RDF values at 2 mA stimulation were $54.0 \pm 15.8\%$, $49.6 \pm 16.4\%$ and $8.9 \pm 4.3\%$ (percentage of SEP in left, contralesional S1fl during right, unaffected forelimb stimulation; mean \pm SEM), at 2, 3 and 24 h after permanent MCA-O, respectively. At 24 h after transient MCA-O, RDF in ipsilesional S1fl was $4.9 \pm 3.2\%$.

We also detected electric activity in contralesional S1fl when the affected forelimb was stimulated. At 2 and 3 h post-stroke, contralesional (left) RDF values at 2mA stimulation of the affected (left) forelimb were $15.6 \pm 6.9\%$ and $11.5 \pm 3.5\%$, respectively. These RDF values were diminished at 24 h post-stroke (permanent stroke: $5.5 \pm 1.8\%$, transient stroke: $5.9 \pm 2.5\%$).

Discussion

Our study demonstrates that electrical activity in S1fl is partially preserved at 2-3 h after permanent MCA-O, but has largely disappeared at 24 h after both transient and permanent MCA-O. The latter is in agreement with lack of fMRI activity in S1fl during the first days after stroke in rats.^{1,2} Furthermore, contralesional activation responses upon stimulation of the affected forelimb, as observed in this electrophysiology study, have also been described in fMRI studies in rat stroke models.^{1,2} Thus, stroke-induced changes in fMRI-detected brain activation, which are based on measurement of hemodynamic responses, correlate with changes in electrophysiological activity.

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TITLE**TYPE III NEUREGULIN 1 SIGNALING IN PREFRONTAL CORTICAL NEURONS****AUTHORS**

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ABSTRACT

Neuregulin 1 (Nrg1), a schizophrenia-susceptibility gene, is involved in many aspects of neural development such as migration and differentiation of neurons and glia as well as modulation of neurotransmission. Type III Nrg1 heterozygous (+/-) mice show distinct behavioral phenotypes including sensory motor gating deficits and impaired performance in short term memory tasks. In addition, nicotinic-mediated glutamatergic transmission is altered between synapses from ventral hippocampus (+/-) to nucleus accumbens (nAcc) (+/+). Neurons in the prefrontal cortex (PFC), an area critical for working memory, express type III Nrg1. PFC layer 5 neurons project to the nAcc. We hypothesize prefrontal cortical circuits are impaired in Nrg1 heterozygous mice. To determine the role of type III Nrg1 in PFC, we assess the morphology of PFC layer 5 pyramidal neurons by modified Golgi impregnation technique and immunohistochemistry. The effect of Nrg1 deficits in PFC-nAcc circuits are examined in chimeric cocultures of WT vs. HET vs. KO PFC "micro-slices" and WT nAccs neurons.

KEY WORDS: Neuregulin; PFC; nucleus accumbens; Ca²⁺ signaling; nicotine

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TITLE**CIRCADIAN TEMPERATURE RHYTHMS IN ELDERLY WITH COGNITIVE DYSFUNCTIONS****AUTHORS**

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ABSTRACT:

Elderly often show a change in their circadian temperature rhythm, why these changes occur is yet unclear. To some extent the changes are due to alterations in the vasculature system, but also clock functions of the suprachiasmatic nucleus (SCN) is thought to be of influence. This study investigated whether there are differences in circadian skin temperature rhythms in elderly with different levels of cognitive dysfunctions compared to healthy controls.

46 patients (15 Alzheimer Disease, 11 Mild Cognitive Impairment, 10 Subjective Memory Complaints) and 11 healthy controls participated in the study. Skin temperature (T_{skin}) was measured distally (hands, feet) and proximate (abdomen, shoulders, thighs) for 24 hours (iButtons, ThermoChrome, Maxim Dallas). Missing data was interpolated and aggregated into half hourly averages, then distal and proximal temperatures were averaged. Skin temperature and activity were analysed using two tailed student's t-test, daytime and nighttime separately. Influence of activity on temperature was analysed using a multilevel modelling program to fit an algorithm for the data of a specific group.

During daytime, elderly with cognitive dysfunctions maintained a higher T_{skin} than healthy controls, no differences were found during the nighttime. Differences could not be explained by activity levels, these did not differ between groups. Differences in T_{skin} were influenced by the position change from supine to upright, and when activity levels increased. A higher daytime T_{skin} suggests an increased risk of heat loss to the environment and consequently a lower daytime core temperature (T_{core}). Results further indicate that elderly with cognitive dysfunction may have an attenuation in the sympathetic vasoconstrictive response to an upright position.

KEY WORDS: Temperature, circadian, Alzheimer, MCI, activity

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TITLE

ESTIMATION OF IMAGE DERIVED INPUT FUNCTIONS USING A RECONSTRUCTION BASED PARTIAL VOLUME CORRECTION ALGORITHM: METHODOLOGY AND EVALUATION IN [¹¹C]FLUMAZENIL STUDIES

AUTHORS

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ABSTRACT

Introduction

The availability of image derived input functions (IDIF) obviates the need for arterial blood sampling and thereby facilitates clinical use of quantitative PET studies. The aim of this study was to develop a method for deriving IDIFs using reconstruction-based partial volume correction (PVC) [1].

Methods

PET and arterial blood data from nine dynamic [¹¹C]flumazenil scans, acquired using an ECAT EXACT HR+ scanner and an on-line blood sampler, were used to develop and evaluate the method. Scans were reconstructed using both standard (no PVC) ordered subset expectation maximization (OSEM, 2 iterations, 16 subsets) and a PVC-OSEM algorithm, which corrects for the spatial resolution of the scanner. Number of iterations and width of PVC kernel were varied.

The following regions of interest (ROIs) methods were evaluated for defining cerebral arteries: (a) pixel value threshold, (b) variable number of 'hottest' pixels per plane, (c) region growing, (d) cluster analysis, and (e) MR-based ROI. ROIs were defined on a pseudo blood volume image, generated by summation of early frames (<60s). ROIs were copied to all frames and IDIFs were extracted from both OSEM and PVC-OSEM images. For each IDIF the following parameters were derived: (a) area under the curve (AUC) for peak (1-2 min), (b) AUC for tail (2-60 min), (c) volume of distribution (V_d) obtained from parametric Logan images, and (d) V_d and K_1 obtained from parametric basis function method (BFM) images. In each case, results were compared with those using on-line measured arterial input functions.

Results

For PVC-OSEM, the optimal trade-off between computational time and signal-to-noise ratio was obtained for 4 iterations and 16 subsets. A 5.5 mm Gaussian resolution kernel gave optimal recovery correction. The best IDIF was obtained using the 'four hottest pixels per plane' over the blood pool in the region below the base of the skull. Compared with standard OSEM, use of PVC-OSEM improved mean (SD) AUC from 0.46 (0.06) to 1.15 (0.11) for the peak and from 0.82 (0.06) to 0.94 (0.12) for the tail part of the input function, respectively. Results of the comparison between OSEM and PVC-OSEM for V_d and K_1 are shown in Table 1 and Figure 1.

Discussion and conclusions

Excellent correlations were obtained between V_d and K_1 values based on IDIFs and those based on on-line sampled input functions. Definition of an accurate IDIF may be sensitive to patient movement and future studies need to focus on motion correction methods. Nevertheless, this study shows the feasibility of deriving accurate IDIFs from dynamic PET scans using reconstruction-based PVC.

[1] Reader et al., IEEE-TNM 50:1392-1397; 2003

KEY WORDS: Positron emission tomography, image derived input function, partial volume correction, reconstruction

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	Logan V_d		BFM V_d		BFM K_1	
	OSEM	PVC-OSEM	OSEM	PVC-OSEM	OSEM	PVC-OSEM
Slope	1.38 (0.11)	1.02 (0.10)	1.42 (0.25)	1.10 (0.18)	1.90 (0.72)	0.84 (0.18)
intercept	0.06 (0.04)	-0.01 (0.02)	0.10 (0.27)	-0.02 (0.17)	0.21 (0.13)	0.03 (0.06)
R^2	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	0.78 (0.18)	0.91 (0.22)

Table 1 – Mean (SD) slope, intercept and correlation coefficient (R^2) for Logan V_d and BFM V_d and K_1 . Results are given for IDIF extracted from standard (no-PVC) OSEM and PVC-OSEM.

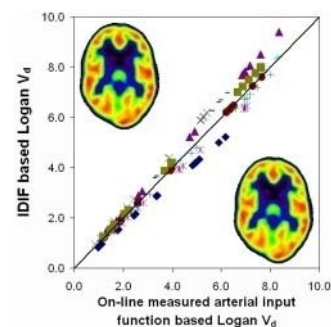


Figure 1 – PVC-IDIF based Logan V_d versus on-line measured arterial input function based Logan V_d for 15 ROIs per subject (n=9). An IDIF and on-line measured arterial input function based Logan V_d image is shown on the y- and x-axis respectively.

TITLE**EARLY MATERNAL SEPARATION INDUCES GENDER DIFFERENCES IN NEUROGENESIS WITHOUT AFFECTING NEWBORN CELL SURVIVAL****AUTHORS**

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ABSTRACT

Stress affects both structure and function of the hippocampus. Adult neurogenesis (the birth of new neurons in the adult brain), is inhibited by stress and exposure to stress hormones. The impact of stress is generally more pronounced when applied in a chronic fashion, or when applied early in life. Of interest, early life stress is a risk factor for the development of stress-related pathologies later in life, like depression. Neurogenesis has furthermore been implicated in the hippocampal volume reductions found in depressed patients and may be involved in antidepressant action. In rats, during postnatal day 3 to 14 of life, maternal behaviour ensures a quiescent, so called "stress-hyporesponsive" period for the pup. This period coincides with postnatal development of the hippocampal dentate gyrus and with maximal levels of neurogenesis. We hypothesized that maternal deprivation at the beginning of this period, a well known early life stressor, will influence neurogenesis and alter the structural make up of the adult hippocampus.

At PND 3, we subjected rat pups to 24 hours of maternal deprivation and labelled dividing cells by BrdU (bromodeoxyuridine) injection. At PND21 we studied both anxiety related behaviour and neurogenesis in these animals. Different phases of the neurogenic process (survival and neuronal differentiation) in both male and female rats were quantified stereologically.

Maternal deprivation on PND3 did not affect anxiety-related behaviour. Additionally, we found no difference in newly generated cell survival (BrdU+ cell number) in both males and females. Analysis of neurogenesis, i.e. double-cortin-positive cell number, revealed an increase in males, but a decrease in females after maternal deprivation.

Maternal deprivation induced gender differences in neurogenesis in the hippocampal dentate gyrus, without affecting newborn cell survival, dentate gyrus volume or anxiety-related behaviour. This points to gender-dependent changes in maturation speed of young neurons, or a difference in cell-fate determination following exposure to early life stress. Possible explanations for this effect are differences in the speed of development of males versus females or differences in maternal care due to the experimental procedure.

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TITLE**TASK DIFFICULTY AND THE ENCODING OF BEHAVIOURAL RELEVANCE IN PRIMARY VISUAL CORTEX****AUTHORS**

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ABSTRACT

Neurons in the primary visual cortex (V1) do not only encode simple features, such as the orientation of a line element, but also the behavioural relevance of objects. For example, when a monkey has to trace a target curve, neuronal responses in V1 evoked by the various segments of this curve are enhanced relative to responses evoked by another, irrelevant curve.

However, the coding of behavioural relevance is not a function of a single neuron but of a whole population. Here we ask how faithfully different interpretations of the same stimulus are reflected in groups of neurons.

We recorded neuronal activity in area V1 while monkeys performed a contour-grouping task in which they needed to group together all contour segments of a target curve and ignore the segments of a distracter curve. Importantly, whether the curve in a neuron's receptive field (RF) was a target or distracter could only be inferred from a location away from the RF, so that the stimulus inside the RF was identical across conditions. To manipulate task difficulty we varied the distance between curves and introduced an intersection in some of the stimuli. The monkey made more errors with increased task difficulty allowing us to study the activity during these error trials.

We will present results on how the activity of groups of neurons reflects behavioural relevance, the effect of task difficulty on activity, and how errors are reflected in population responses.

KEY WORDS: Task difficulty, neural code, V1

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TITLE**DIFFERENCES IN MEMORY CONSOLIDATION IN INBRED MOUSE STRAINS****AUTHORS**

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ABSTRACT

There is a growing agreement on the substantial role of gene- environment interaction in the etiology of psychiatric disorders. In this project, various inbred strains are being used to delineate the genetic components of the gene-environment interaction that determines memory consolidation. Because inbred mouse strains are a retrievable pool of isogenic information, they are powerful sources to identify biological determinants of normal and pathological behaviors using genetical, genomical and behavioral analyses. C57BL/6J and DBA/2J are among the best-studied inbred strains and the recombinant inbred strains derived from them are widely used for quantitative trait loci (QTL) analysis.

The C57BL/6J and DBA2/J inbred strains are known to display differences in emotional learning and anxiety responses, due to functional differences in their hippocampal formation. Although it is known that protein synthesis is involved in this process, the key regulators of memory consolidation as well as memory retrieval are largely unknown. This project aims at assessing the type and time-course of proteins actively involved in memory consolidation, reconsolidation and retrieval within different parts of the hippocampus using a hippocampus-dependent learning strategy. First, we assessed the difference in memory consolidation by measuring freezing behavior at different time points after conditioning mice in the fear-conditioning paradigm. A proteomics analysis approach will be used to capture proteins present in the synaptic membrane compartment shortly after conditioning, and expression differences that coincide with the capability of emotional learning will be further examined. At present, tissue has been collected.

In order to capture genes involved in memory consolidation, a gene expression analysis was carried out at different time points after re-exposure to the previously conditioned context. Emphasis has been put on AMPA receptors and their interactors. The aim is to find key regulators involved in hippocampal memory formation and consolidation in order to use them for viral-mediated intervention.

KEY WORDS: Inbred mice, memory consolidation, fear conditioning, real time quantitative PCR, AMPA receptor, hippocampus

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TITLE**MLC1 IS ASSOCIATED WITH THE DYSTROPHIN-GLYCOPROTEIN COMPLEX AT ASTROCYTIC ENDFEET****AUTHORS**

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ABSTRACT

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a progressive cerebral white matter disease with onset in childhood, caused by mutations in the MLC1 gene. MLC1 is a protein with unknown function that is mainly expressed in the brain in astrocytic endfeet at the blood-brain and cerebrospinal fluid-brain barriers. It shares its localization at astrocytic endfeet with the dystrophin-associated glycoprotein complex (DGC). The objective of the present study was to investigate the possible association of MLC1 with the DGC. To test this hypothesis, (co)-localization of DGC-proteins and MLC1 was analyzed by immunohistochemical stainings in gliotic brain tissue from a patient with multiple sclerosis, in glioblastoma tissue and in brain tissue from an MLC patient. In control tissue a direct protein interaction was tested by immunoprecipitation. Results revealed that MLC1 is co-localized with DGC-proteins in gliotic brain tissue. We demonstrated that both MLC1 and aquaporin-4, a member of the DGC, were redistributed in glioblastoma cells. In MLC brain tissue, we showed absence of MLC1 and altered expression of several DGC-proteins. We demonstrated a direct protein interaction between MLC1 and Kir4.1. From these results we conclude that MLC1 is associated with the DGC at astrocytic endfeet.

KEY WORDS: MLC1, astrocytes, endfeet, dystrophin-associated glycoprotein complex, leukodystrophy

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TITLE**THE GENETICS OF SYMPTOM DIMENSIONS OF SCHIZOPHRENIA: REVIEW AND META-ANALYSIS****AUTHORS**

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ABSTRACT**Background**

The use of symptom dimensions of schizophrenia as quantitative phenotypes can reduce the heterogeneity of schizophrenia and as such facilitate genetic research. However, the heritability of symptom dimensions is not established.

Aims

We aim to investigate whether the symptom dimensions reality distortion, psychomotor poverty and disorganization are heritable phenotypes of schizophrenia.

Method

We performed a Medline search including all papers from 1980 to 2007. In addition to reviewing the articles, we investigated the possibility to perform meta-analyses on these studies.

Results

We identified 25 relevant papers. Only the studies on schizophrenia affected sibling pairs were suitable for meta-analysis. Both twin, adoption and affected sibling studies consistently demonstrate a genetic contribution to the disorganization dimension. These studies do not unequivocally support a large genetic contribution to neither the reality distortion symptom dimension nor to the psychomotor poverty symptom dimension. In contrast several molecular genetic studies did report gene associations to psychomotor poverty.

Conclusions

These data carefully suggest that only the disorganization symptom dimension may provide a useful alternative phenotype for genetic research. This analysis is limited by the scarcity of twin and adoption studies available for estimating heritability of symptom dimensions.

KEY WORDS: Schizophrenia, symptom dimensions, heritability, genetics, meta-analysis

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TITLE**THE EFFECT OF MATERNAL CARE ON THE DEVELOPMENT OF CORTICAL LAYER 2/3 PYRAMIDAL NEURONS: A LINK WITH REELIN****AUTHORS**

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ABSTRACT

Natural occurring variations in maternal care which can be defined as pup licking and grooming (LG) and arched-back nursing (ABN) have a persistent effect on response to stress and cognitive development in offspring. Recently, it has been shown that in the hippocampus of high LG-ABN rats the mRNA levels of reelin, a glycoprotein which plays an important role in hippocampal and cortical development, are elevated. In the hippocampus, reelin promotes dendritic maturation. Here we show that, in the cortex, reelin levels are also increased in high LG-ABN rats. However, in contrast to the hippocampus, dendritic complexity of layer 2/3 pyramidal neurons in the cortex is reduced. Furthermore, we show that the total spine frequency of these neurons is reduced.

KEY WORDS: Maternal care, cortical layer 2/3 development, reelin

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TITLE**IDENTIFICATION OF MOLECULAR TARGETS FOR IMPROVEMENT OF CELL GRAFT FUNCTION FOR TREATMENT OF SPINAL CORD INJURIES****AUTHORS**

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ABSTRACT

Regeneration of damaged axons and restoration of function is rarely successful after spinal cord injury (SCI). Transplantation of specific cell types at the site of the lesion after injury is one of the most promising therapies. Still, efficacy of the different cell types currently used to optimally promote repair of SCI is highly debated. Moreover, the molecular mechanisms underlying the beneficial effects these cells might have on regeneration are largely unknown. An understanding of these growth-promoting mechanisms will be essential for the development of future treatments of SCI. Therefore, this study has two specific aims:

- Aim 1. Determine the relative efficacy of the different cellular graft types used in cell therapy for SCI by comparing the functional improvement in a specific experimental paradigm.

- Aim 2. Identify molecules responsible for the differences between cell types in functional outcome using medium-throughput neurite outgrowth and cell-cell interaction bioassays.

Results obtained along aim 1: We have set up cultures of five different cell types, which are widely studied as cell transplants in SCI: olfactory ensheathing glia (OEG), Schwann cells (SC), fibroblasts, GRP derived astrocytes (GAD), and bone marrow stromal cells (BMSC) These cells will be marked by transduction with LV-GFP and transplanted into a unilateral retinal spinal tract lesion paradigm.

Analysis will comprise: the survival of transplanted cells, test scores on regaining functional recovery, plasticity and the distribution and expression of molecules known to inhibit neuroregeneration.

Presently, frozen stocks of OEG, SC, fibroblasts and BMSC have been prepared.

Results obtained along aim 2: Interaction and growth-promoting properties are proposed to distinguish OEG from other cell types. Our lab has identified genes that could be involved in these mechanisms by a 22K oligo microarray (Agilent) gene expression analysis of OEG in culture and OEG in the regenerating olfactory nervous system. We initially focused on targets potentially involved in cell adhesion, matrix formation, cell migration and axon outgrowth-promotion. This defined a list of 71 target genes. These genes have been functionally validated by siRNA-mediated knockdown studies in medium-throughput *in vitro* bioassays which has resulted in the identification of 14 genes that had an effect on neurite outgrowth of E14 dorsal root ganglion neurons and 10 genes that had an effect on the interaction of OEG or SC with meningeal fibroblasts.

KEY WORDS: Cell graft treatment, spinal cord injury, molecular targets for enhancement, medium throughput *in vitro* siRNA screen

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TITLE**SELECTIVE SLOW-WAVE-SLEEP DEPRIVATION INDUCES LAPSES OF ATTENTION IN PSYCHOMOTOR VIGILANCE TASKS****AUTHORS**

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ABSTRACT

Loss of sleep leads to reduced vigilance. We investigated the effect of partial sleep deprivation in healthy well-sleeping elderly on two tasks of psychomotor vigilance, one requiring an immediate response to the target stimulus and the other requiring a decision before responding. We developed a slow-wave-sleep selective sleep deprivation procedure, using auditory stimuli delivered to the subject based on the slow-wave density in the EEG of the subjects: We recruited 13 healthy well-sleeping elderly subjects who spent two nights in the sleep laboratory while we recorded their polysomnogram; we repeated the measurement with an interval of 5-7 weeks. On one of the occasions, balanced across subjects, we administered partial sleep deprivation for two consecutive nights. On each of the sessions we administered the two vigilance tasks on separate days, in a balanced order across subjects. Selective sleep deprivation in healthy well-sleeping subjects resulted in a higher number of vigilance lapses across the two tasks, but not in a change in reaction times for the correct responses. Our results corroborate and extend the findings of increased number of lapses after sleep deprivation in healthy young subjects.

KEY WORDS: EEG, vigilance, sleep deprivation

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TITLE**REPEATED EXPOSURE TO A NOVEL ENVIRONMENT; EVALUATING THE ADAPTIVE CAPACITY IN THE BALB/C AND 129/J MOUSE STRAIN****AUTHORS**Amber R. Salomons, S.S. Arndt, F.Ohl**DEPARTMENT/INSTITUTE**

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ABSTRACT

Anxiety refers to a biologically relevant response and is adaptive in its nature. When anxiety responses are inappropriate or prolonged i.e. non-adaptive, they can lead to long lasting (neuro) physiological changes and finally to various forms of pathological anxiety. In animals anxiety might be defined as pathological if it appears to lack adaptive value and severely interferes with normal interaction of the sufferer with its physical and social environment. In this experiment we aimed at evaluating whether the highly anxious phenotype of BALB/c mice represents a pathological, i.e. non-adaptive form of anxiety. We investigated 2 inbred mouse strains, the BALB/c and the 129/J male mice and tested them 40 times (4 trials/day) for 5 minutes per trial in the modified hole board test. The results show that the BALB/c mice initially demonstrated significantly more avoidance behaviour as well as risk assessment than 129/J mice. The initially higher anxious BALB/c individuals subsequently habituated to the test situation, and showed increased escaping behaviour. In contrast, the 129/J strain starting at a lower anxious level than the BALB/c mice, showed no habituation in avoidance behaviour throughout the test period. Habituation in BALB/c mice was also seen in other parameters such as exploratory activity and locomotion whereas no apparent changes in these parameters were observed in the 129/J strain during the test period. Notably, stress hormone (corticosterone) responses to the initial test situation revealed higher corticosterone levels in BALB/c mice compared to 129/J mice. This underlines that the BALB/c strain habituates to an initially stressful novel environment while the 129/J strain probably lacks adaptive capacity under the same circumstances. Further investigations are necessary to show whether 129/J mice are either insensitive for the aversive characteristics of a novel environment or might be a model for impaired habituation.

KEY WORDS: Pathological anxiety, inbred mice, modified hole board, habituation**TELEPHONE-NUMBER:** 030-2534149**E-MAIL-ADDRESS:** a.r.salomons@uu.nl

TITLE**CRB2 cKO, WHAT IS THE ROLE OF CRB2 IN THE RETINA?****AUTHORS**Alicia Sanz Sanz, R. Vos R, J. Wijnholds**DEPARTMENT/INSTITUTE**

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ABSTRACT

The establishment and maintenance of cell adhesion and apical-basal polarity in the retinal epithelia requires the presence of specific evolutionary conserved protein complexes at the adherens junctions and adjacent areas. Crb1 and its family member Crb2, are highly homologous transmembrane proteins that co localize at the so-called subapical region (SAR), just above the adherens junctions at the outer limiting membrane (OLM), where they organize intracellular scaffold protein complexes.

Mutations in the CRB1 gene are associated with several kinds of retinopathies such as Leber congenital amaurosis and progressive types of retinitis pigmentosa (e.g. RP12).

Loss of Crb1 in mice leads to loss of adhesion between Müller glia cells (MGC) and photoreceptor cells (PRC) at foci, followed by disorganization and degeneration of the retina. The high similarity in protein structure of Crb1 and Crb2 and their co localization at the SAR point a possible overlap or competition in function, however redundant functions of these proteins are not known yet.

Electron microscopy showed localization of Crb2 in both Müller glia cells and photoreceptor cells. Recombination-mediated genetic engineering was used to generate a *Crb2* conditional knock out construct. Studies of the phenotype of the retina- conditional *Crb2* knock out mice will be performed in order to unravel the role of Crb2 in neuron (PRC) -glia (MGC) adhesion and apical-basal polarity.

KEY WORDS: Crb1, Crb2, retina, SAR, cell adhesion, cell polarity**TELEPHONE-NUMBER:** 020-5664687**E-MAIL-ADDRESS:** a.sanz@nin.knaw.nl

TITLE**LONG-TERM DELAY OF PUBERTY BY TREATMENT WITH GNRH-ANALOGUES AND THE EFFECT ON BONE MINERAL DENSITY (BMD) IN TRANSSEXUAL ADOLESCENTS****AUTHORS**

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ABSTRACT

During puberty, bone growth and mineralization as well as bone turnover increase dramatically. Skeletal bone mass reaches over 90% of its maximum by age 18 but does not peak until age 25-30. Biologically delayed puberty may have an adverse relationship with adult BMD although these results are inconsistent. In both male and female patients with central precocious puberty, the abnormal onset of puberty and the long-term GnRH-analogue treatment do not impair the achievement of peak bone mass.

In this study the effect on BMD of long-term treatment with GnRH-analogues alone and in combination with cross-sex hormones is investigated. Transsexual adolescents of the VU university medical center and diagnosed according to the DSM-IV criteria are being treated with GnRH-analogues from the age of 12 and from Tanner stage B2/ G2-3 to suppress endogenous gonadal stimulation and to prevent irreversible characteristics of the unwanted sex. From the age of 16 years cross-sex hormones are added to the GnRHa-medication.

At this moment sixty-one patients have been treated with a GnRH-analogue alone with a mean duration of 17,9 months (range 0-48 months). In 37 cross-sex hormones were added with a mean duration of 17,6 months (range 0-45 months) from the age of 16 years. During treatment a decrease in height velocity and bone maturation was observed. The duration of the GnRH-analogue treatment did not result in significant effects on BMD during and after treatment with cross-sex hormones.

Total bone density in gram/cm^2 remained in the same range during long-term suppression of puberty, while the BMD z-score for calendar age slightly decreased. On cross-sex steroid hormone treatment total bone density significantly increased, while the z-score remained in the same range. In conclusion: During GnRHa-treatment bone development slows down. During cross-sex steroids bone density appears to catch up.

KEY WORDS: Bone mineral density, transsexual adolescents, puberty delaying treatment, cross-sex hormones

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TITLE**PHYSICAL ACTIVITY AND CARDIOVASCULAR FITNESS IN PATIENTS WITH SCHIZOPHRENIA****AUTHOR**

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ABSTRACT**Background**

The amount of physical activity and level of cardiovascular fitness appear to be low in patients with schizophrenia. Patients with schizophrenia are at a high risk of developing somatic co-morbidities which in turn cause a reduced life expectancy. Almost no studies specifically focus on physical activity and cardiovascular fitness in these patients.

Objectives

This study has three objectives. The first two objectives are to determine the amount of physical activity and level of cardiovascular fitness in patients with schizophrenia as compared to matched healthy controls. The third objective is to assess the relationship between physical activity and cardiovascular fitness data.

Methods

The amount of physical activity was determined by means of the Sensewear[®] Armband, which 14 patients (age=26.9±6.8) wore for 3 bouts of 24 hours. A group of 20 subjects (age=24.9±3.6) from a TOPFIT pilot study served as controls. The level of cardiovascular fitness was determined by means of a Maximal Exercise Tolerance Test in 6 patients (age=30.0±7.0).

Results

Patients were significantly less physically active than controls ($\alpha=1\%$). Duration of sleep and lying down was significantly longer in patients as compared to controls ($\alpha=1\%$). The difference in Total Energy Expenditure (TEE) between groups was nonsignificant. When comparing to healthy controls, resting Metabolic Rate (RMR) in patients was higher ($\alpha=5\%$). Cardiovascular fitness data showed low $\dot{V}O_{2-max}$ (mean=33.6 ml/kg/min) and HR_{max} (mean=173.8 b/min) data when compared to the healthy population. Resting heart rate (HR_{rest}) in patients was 77 b/min. There was a strong and significant correlation between $\dot{V}O_{2-max}$ and the average METs expended ($r=1.0$), and between $\dot{V}O_{2-max}$ and duration of inactivity ($r=-0.9$).

Discussion

Patients are less physically active than healthy controls. The low $\dot{V}O_{2-max}$ and HR_{max} results and the high HR_{rest} in patients indicate a lower level of cardiovascular fitness as compared to the healthy population. The level of cardiovascular fitness was positively correlated with the amount of physical activity, but these results should be interpreted cautiously. The power of the cardiovascular fitness data of this study is limited. One limitation is the small group of patients, which makes generalizability of cardiovascular fitness data difficult. Due to time limits, a healthy control group was not available for the cardiovascular fitness part of this study.

Clinical implications

Given the low amount of physical activity undertaken and the level of cardiovascular fitness in patients, regular physical exercise should have a positive effect on health in patients with schizophrenia. Future research should focus on exercise interventions in this group of chronic psychiatric patients. A reliable comparison of cardiovascular fitness data and other relevant aspects of physical health, like metabolic factors, between patients and healthy controls is also necessary.

KEY WORDS: Physical activity; cardiovascular fitness; schizophrenia; SenseWear[®]; METT

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TITLE**ROLE OF MUNC13 IN NEURONAL DENSE CORE VESICLE RELEASE****AUTHOR(S)**

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ABSTRACT

Neuronal dense-core vesicles (DCVs) contain a wide variety of neuromodulatory peptides and hormones involved in many biological processes, ranging from neuronal survival to memory formation. In contrast to synaptic vesicle release, the molecular events underlying DCV secretion are poorly understood. Here we have used a genetically-encoded reporter of dense-core vesicle secretion, Semaphorin 3A (Sema3A), in combination with live cell imaging to study dense-core vesicle release in mouse cortical neurons. To dissect the molecular pathway, we focused on the role of the priming factor Munc13 in targeting and release of DCVs. Release of Sema3A coupled to pH-sensitive EGFP was compared in wild-type, Munc13-1/-2 double knock-out and Munc13-1 overexpressing neurons. Here we show that in contrast to synaptic vesicles, Munc13 is not essential for DCV release but is capable of increasing DCV release if overexpressed. These results suggest a different requirement for synaptic proteins in DCV secretion compared to synaptic vesicle release.

KEY WORDS: Dense-core vesicles, release, Munc13

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TITLE**NOVEL ANIMAL MODEL FOR FEMALE SEXUAL DYSFUNCTION****AUTHORS**

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ABSTRACT

Female Sexual Dysfunction (FSD) affects 43% of all adult women. These problems can be categorized in desire disorder (22%), arousal disorder (14%) and pain associated with sexual interaction (7%).

Currently, no animal model for FSD is available. Based on our successful model for Male Ejaculatory Disorders, we hypothesize that a number of female rats will display stable, abnormal sexual behaviour. These females might be useful in the testing of new treatments for FSD.

110 Sexually experienced, intact, estradiol-primed female rats were placed in an empty compartment adjacent to a compartment with a male. The females were allowed to switch between the compartments via a hole through which only the females could fit. During 30 minutes, the time spent in the female (empty) compartment and both male and female sexual behaviour were scored.

In the first test, 41 females (37%) strongly preferred the female compartment (>20 minutes). 8 of these "male-avoiders" were selected for a second and third test, together with 12 "male-approachers" (<10 minutes in female compartment).

The sexual behavior of the selected females was highly stable over 3 tests, suggesting the existence of different endophenotypes in female rats. The avoiders did hop and dart in the female compartment (although significantly less than the approachers in the male compartment), what could indicate that receptivity was successfully induced.

In conclusion, the stable, male-avoiding behavior of some females might correspond to the characteristics of women with FSD. Therefore, these avoiders are a promising new model for Female Sexual Dysfunction, specifically for sexual desire and/or arousal disorders.

KEY WORDS: Sexual behavior, female rats, animal model, endophenotypes, female sexual dysfunction

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TITLE**THE ROLE OF THE GABA_AR SUBUNIT α 1 AND THE GABAERGIC INHIBITORY SYSTEM IN MOLECULAR VISUAL PLASTICITY****AUTHORS**

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ABSTRACT

The visual cortex is a layered structure where thalamocortical LGN projections, that receive input from both eyes, innervate layer 4 neurons.

The initial establishment of the circuitry is independent of visual experience, but postnatal week 4-5 in the mouse visual cortex is a so called 'critical period' (CP) for experience dependent modifications.

When one eye is closed during the CP, the cortex becomes more responsive to the open eye relative to the closed eye. This shift in responsiveness is absent in the pre- and post critical period.

It is known that the maturation of the inhibitory circuitry results in the initiation of the critical period. With reduced GABAergic transmission due to a deficient form of GABA synthesizing enzyme GAD65, the critical period is not initiated until transmission is increased with benzodiazepines, which are allosteric agonists for GABA_A receptors. Also, infusion of *Zolpidem*, a non-benzodiazepine selectively binding to the α 1 subunit of the GABA_A receptor, is able to prematurely initiate an ocular dominance shift after monocular deprivation.

Mice with a mutation in the *Zolpidem* binding site in the α 1 subunit cannot initiate a premature shift with *Zolpidem*, although this is able in animals with the same mutation during CP.

This suggested a role for the α 1 subunit of GABA_AR in the plasticity of the visual cortex. α 1 differs from other GABA_AR subunits in that it mediates faster kinetics and that it is present at sites innervated by perisomatic puncta. We wanted to investigate how these two properties of α 1 play a role in ocular dominance plasticity, and how they are changed when α 1 is absent.

With *in vivo* optical imaging of an intrinsic signal in a knock-out line for the α 1 subunit, we measure ocular dominance plasticity and acuity in the cortex to see if α 1 is necessary for opening a critical period.

This experimental set-up transcranially measures the blood flow of the visual cortex (V1) upon different visual stimuli of the eyes.

Additionally we wanted to know if in these knock out animals there is a change in the perisomatic innervation of pyramidal cells, accounting for functional differences.

We are analyzing perisomatic inhibitory innervation in different layers of V1 using specific antibodies for NeuN and parvalbumin (PV). PV is a marker for GABAergic basketcells and present in presynaptic boutons opposing α 1 subunit containing GABA_ARs on the pyramidal soma, forming a characteristic *puncta ring*. We will establish whether this innervation is changed compared to control animals.

We will also stain for other associated proteins like PSA-NCAM, α 2 subunit, perineuronal net components and for GFP in *in utero electroporated* animals. For further functional analysis we will also look at the maturation of the visual acuity in KO and control animals.

KEY WORDS: Visual, plasticity, critical period, inhibitory, GABA, α 1

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TITLE**ROLE OF MACROPHAGES IN PERIPHERAL NERVE DEGENERATION****AUTHORS**

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ABSTRACT

Secondary axonal damage is a major determinant of disability in peripheral nerve diseases. During the normal process of Wallerian degeneration (WD) macrophages will accumulate in the injured nerve. Previous research showed an effect of complement inhibition on the regeneration of the peripheral nerve after WD. We have shown that deficiency/inhibition of the complement system decreases the number of endoneurial macrophages, delays WD and facilitates regeneration after injury¹. To determine the direct role of macrophages during WD we treated WT rats with clodronate-liposomes, Clodronate-liposomes deplete haemotogenous macrophages. At 3 days post- injury, the clodronate-treated rats showed a decrease in the number of macrophages inside the endoneurium, which appeared small compared to the PBS-treated controls, suggesting lack of activation. Myelin morphology was conserved in the clodronate-treated animals compared to controls. These results suggest that macrophages are responsible for rapid structural damage to the nerve after injury.

Reference

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KEY WORDS: PNS, Wallerian degeneration, macrophages, innate immunity

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TITLE
STRIATAL SUBSTRATES OF COCAINE TAKING

AUTHORS

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ABSTRACT

There is a wealth of evidence showing that dopamine neurotransmission in the nucleus accumbens is of great importance for the reinforcing effects of psychostimulant drugs. Recent studies have suggested that other subregions of the striatum might be involved in other aspects of cocaine self-administration. For example, the dorsolateral striatum has been associated with the well-established or habitual aspects of cocaine seeking. Here, we tested the hypothesis that in animals with limited drug experience, the ventral part of the striatum is more important for cocaine self-administration than the dorsal striatum.

Rats were trained to self-administer cocaine (0.25 mg/inf) under a fixed-ratio 1 schedule of reinforcement. After responding had stabilized (usually within 6 - 14 sessions) rats received micro-infusions with different doses of the dopamine receptor antagonist α -flupenthixol into subregions of the striatum.

Infusion of α -flupenthixol into the nucleus accumbens core and olfactory tubercle did not affect cocaine self-administration, suggesting that dopamine neurotransmission in these regions is not critically involved in cocaine self-administration. Cocaine intake decreased, when α -flupenthixol was administered into the nucleus accumbens shell, suggesting a reduced motivation to take cocaine. Surprisingly, infusions of α -flupenthixol into the dorsolateral striatum dose-dependently increased cocaine intake. This suggests that after limited drug experience, α -flupenthixol in the dorsolateral striatum decreased the reinforcing properties of cocaine and perhaps, at this stage, that cocaine taking already has acquired habitual properties. In conclusion, dopaminergic neurotransmission in the nucleus accumbens shell and the dorsolateral striatum plays an important, but distinct role in cocaine self-administration in rats with limited cocaine experience.

KEY WORDS: Addiction, dopamine, striatum

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TITLE**ACCURACY OF VARIOUS 3D-OSEM VERSUS 3D-FBP RECONSTRUCTIONS OF HRRT PET STUDIES****AUTHORS**

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ABSTRACT

The High Resolution Research Tomograph (HRRT, CTI/Siemens, Knoxville, TN, USA) is a dedicated human brain positron emission tomography (PET) scanner. Due to scanner geometry, gaps are present between the detector heads, leading to missing data in sinograms. These missing data need to be estimated by gap filling methods in case of 3D filtered backprojection (FBP) reconstruction. Amongst others this is one of the reasons that reconstruction methods that do not require additional corrections for missing data, such as iterative reconstruction methods, have been preferred for reconstructing HRRT studies so far. Recently, a fully 3D ordinary Poisson ordered subsets expectation maximization (OP-OSEM) reconstruction method has been implemented to improve the bias. Further improvement might be expected using a new randoms estimation method based on coincidence histograms. The goal of this study is to evaluate the currently available and recommended 3D OSEM reconstruction techniques for the HRRT for their quantitative accuracy under clinical conditions. They will be compared with (so far unavailable) in-house developed analytical 3D-FBP reconstruction. To this end several phantom studies and a human brain study were performed.

OP-OSEM using calculated randoms performed most accurately compared with OP-OSEM using measured randoms and/or with ANW-OSEM for most phantom (within 6%) and clinical studies. However, both positive and negative biases in reconstructed activity concentrations and large biases in grey and white matter contrast (up to 41%) were still observed as function of scan statistics (e.g. at high noise levels). Moreover OP-OSEM with calculated randoms also showed bias up to 16% in clinical data, *i.e.* in some pharmacokinetic parameters as compared with those obtained with 3D-FBP. Therefore, 3D-FBP should be used to assess the accuracy and validate use of OSEM reconstructions of clinical HRRT PET studies.

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KEY WORDS: Positron emission tomography, image reconstruction, maximum likelihood estimation

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TITLE**AN *IN VITRO* MODEL FOR SPECIFIC DE- AND REMYELINATION USING WHOLE BRAIN SPHEROID CULTURE****AUTHORS**

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ABSTRACT

The model most often used to study demyelination occurring in MS is the experimental autoimmune encephalitis (EAE) model. This model has a few major drawbacks. First, demyelination is relatively limited in EAE. Second, large numbers of animals are necessary. Finally, the involvement of the immune system in the development of EAE makes it very difficult to differentiate the contributions of the different cell types. Therefore, a reproducible *in vitro* model for de- and remyelination is necessary. The aim of this study was to develop a specific *in vitro* demyelination model using lysophosphatidyl choline (LPC) in whole brain spheroid cultures. The neuronal and glial cell types present in this model form three-dimensional contacts, leading to multilayered myelin around axons.

Methods: Using the spheroid culture system we investigated the characteristics of demyelination based on repeated exposure to LPC. LPC and various drugs were added 3 times a week. After one week of treatment medium was replaced and the spheroids were left to recover for a week to allow remyelination.

Results: Decreased myelin basic protein (MBP) staining and concentration (~ 50% reduction) was observed after 1 week of exposure to LPC. Additionally the concentration of 2',3', cyclic nucleotide 3'-phosphodiesterase (CNPase) activity was down to 70% after one week. These results are indicative of demyelination, which was confirmed by electron microscopy. After one week of recovery the MBP staining normalised, as did the CNPase activity, suggestive of remyelination. The source of the remyelination could be oligodendrocyte precursors present in our spheroid cultures, as seen by NG2 staining. The number of precursors was decreased after exposure to LPC, but they are still present. We studied the role of oxygen radicals and membrane cholesterol contents in the demyelination caused by LPC. MBP staining and concentration were normalised and also CNP-ase activity was comparable to control when spheroids were treated with vitamin E, Simvastatin or cholesterol. Conclusions: The protective effect of vitamin E, simvastatin and cholesterol against LPC toxicity may be explained by the decline in LPC induced ROS generation in myelin and loss of membrane integrity. The specific de- and remyelination observed in this *in vitro* model supports the use of this model in research into the mechanisms of remyelination in MS. Furthermore, this model can be used in preclinical drug or cell transplant testing for remyelination, reducing the number and discomfort of animals.

KEY WORDS: Demyelination, whole brain spheroid cultures, remyelination, lysophosphatidylcholin

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TITLE**TOWER AND HOURGLASS:TWO MOTOR BEHAVIOUR TESTS FOR MARMOSET****AUTHORS**Nelleke Verhave, M.J. Jongsma, R.A.P. Vanwersch, S.A.M. Van Vliet, I.H.C.H.M. Philippens**DEPARTMENT/INSTITUTE**

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ABSTRACT

The common marmoset (*Callithrix jacchus*) is a commonly used behavioral model for several motor disorders, under which the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model for Parkinson's disease. Injection with MPTP will result in substantia nigral cell death, which in turn will induce akinesia, rigidity and postural abnormalities in the marmoset. Two new non invasive tests have been developed to evaluate the motor capacity, the Tower test and the Hourglass test.

Initiation of movement effected by the akinesia and rigidity is tested in the tower test.

MPTP lesioned animals are still able to move around in their cage (climbing) however there jumping ability seems so be specifically effected, due to difficulties initiating movement. The aim of the Tower test is to evaluate jumping behavior.

Rigidity caused by the lesions, is tested in the Hourglass test. Animals lesioned with MPTP become very rigid in their movements and seem to have trouble moving around in small spaces. The aim of the hourglass test is to evaluate the animal's flexibility in a confined space.

The results in both tests show a large difference between vehicle and MPTP lesioned animals. Parkinsonian animals do not reach the higher levels of the Tower and take more time to jump to the different levels than the non treated animals. The Hourglass test shows subtle differences between L-DOPA (symptom) treated lesioned animals and non-treated MPTP animals.

In conclusion we present two new sensitive test apparatus to evaluate motor behavior in MPTP lesioned marmosets. We expect that these tests can also be of much use in other marmoset models for diseases that contain motor impairment (e.a. Huntington's disease, Multiple Sclerosis and Stroke).

KEY WORDS: Behavior, marmoset, Parkinson's disease, MPTP, motor behaviour and motor impairment

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TITLE**REWARD-SENSITIVITY IS STRONGER IN STANDARD HOUSED MALE RATS THAN IN ENRICHED HOUSED MALE RATS, WHICH IS INDEPENDENT OF STRAIN****AUTHORS**Mariska Verlaan, J.E. van der Harst, L. Schipper, B.M. Spruijt**DEPARTMENT/INSTITUTE**

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ABSTRACT

Reward-sensitivity is influenced by previous experiences such as stress, and is therefore proposed as a potential animal welfare indicator: Negative experiences induce an increased sensitivity (ie 'need') for reward, and thus, reward-sensitivity can be indicative of the history (previous positive and negative experiences) and welfare state of an animal. This is confirmed by our previous study in Wistar rats in which reward-sensitivity, reflected by anticipatory behaviour to reward, was influenced by previous (standard or enriched) housing conditions. This tool to assess welfare of captive animals on basis of their natural behavioural response in anticipation of a reward seems to have high potential and is further validated in two studies. The main aim of the first study was to establish whether earlier findings of the effect of previous experiences (the history of animals) on reward-sensitivity in Wistar rats can be generalised to other strains. This was investigated by subjecting two rat strains (Wistar and Long Evans), both divided over standard and enriched housing conditions, to a behavioural test to investigate reward-sensitivity: an anticipation-to-reward test. From the anticipation-to-reward test it became apparent that the anticipatory response for the sucrose reward is stronger in standard housed rats than in enriched housed rats, which was independent of the strain. This confirms our earlier finding that standard housing results in an increased sensitivity to reward, which is, as can be concluded from the current study, independent of strain. This indicates that our concept can probably be generalised to other strains.

A second study to further validate anticipatory behaviour to reward is performed. The main aim of this study was to establish whether earlier findings of the effect of previous experiences (the history of animals) on reward-sensitivity in male rats are independent of gender. This was investigated by manipulating the previous experiences of both female and male rats by housing them under standard or enriched conditions. Subsequently, all experimental groups were subjected to an anticipation-to-reward test. This test again confirmed that the anticipatory response for the sucrose reward is stronger in standard housed male rats than in enriched housed male rats, indicating an increased reward-sensitivity in the former group, although the effect was not as strong as in previous studies. Concerning the female rats, this effect of differential housing on reward-sensitivity was less clear. This is in line with earlier reports that behaviour of females is less dependent on previous experiences, which might be similar for experiences in different housing conditions.

Taken into account gender-differences in reward-sensitivity and the effect of previous experiences thereon our concept may have high potential as a welfare indicator for captive animals in general, and may give implications for research that is based on reward-sensitivity- such as addiction studies.

KEY WORDS: Rats, anticipation-to-reward, reward-sensitivity, housing, environmental enrichment, strain, strain-differences, gender, gender-differences**TELEPHONE-NUMBER:** 030-2534149**E-MAIL-ADDRESS:** m.verlaan@vet.uu.nl

TITLE**M1 AND M2 RECEPTOR ACTIVATION ALTERS SYNAPTIC TRANSMISSION OF THE LAYER 5 MEDIAL PREFRONTAL CORTEX****AUTHORS**

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ABSTRACT

Acetylcholine (ACh) is critical for normal cognitive processing in the brain. ACh function in the prefrontal cortex microcircuitry has been investigated to some extent. To understand how ACh alters information processing in prefrontal cortex it is necessary to understand how the balance between excitatory and inhibitory transmission is affected by ACh. Although several depolarizing (Haj-Dahmane and Andrade 1998; Carr and Surmeier 2007) and hyperpolarising effects (Gulledge, Park et al. 2006) of ACh application on the membrane potential of layer 5 medial prefrontal cortical neurons have been reported, it is unknown how excitatory and inhibitory synaptic transmission is affected and what muscarinic receptors are involved. Here, we study this question and find that application of muscarine (10 μ M) strongly increases excitatory glutamatergic and inhibitory GABAergic transmission. This effect is blocked by TTX, showing the dependence on action potential firing in presynaptic neurons. Both glutamatergic and GABAergic synaptic transmission of the layer 5 pyramidal neurons are mainly modulated by M1-type muscarinic receptors. Glutamatergic transmission appears also to be mediated by the M2 receptors, although to a lesser extent. The M2 receptor activation modulates GABAergic transmission in a minority of layer 5 pyramidal neurons. These data show that both excitatory and inhibitory fast synaptic transmission is stimulated by muscarinic receptors and this effect is predominantly mediated by M1 receptors. In future studies, we aim to find out which mouse PFC cell types express these receptors.

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KEY WORDS: Prefrontal cortex, muscarine, synaptic transmission

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TITLE**ROLE OF NMDA-RECEPTORS IN BASELINE AND TASK-RELATED FIRING OF ORBITOFRONTAL CORTEX NEURONS DURING A 2-ODOUR DISCRIMINATION TASK****AUTHORS**

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ABSTRACT

The orbitofrontal cortex (OFC) is thought to guide behaviour on the basis of the cues predicting reinforcers. There is evidence to suggest that firing patterns of OFC neurons reflect the value of a stimulus predicting reward. However, the transmitter mechanisms underlying the formation of these predictive firing patterns remain unknown. One candidate is the glutamatergic neurotransmission system. We recorded activity from OFC neurons in 2 rats in a familiar environment using an electrode array holding 14 independently moveable tetrodes. Additionally, we modified the array to hold a microdialysis probe. Used in reversed operation mode, we unilaterally perfused the OFC during recordings with solutions of N-methyl-D-aspartic acid (NMDA), D-2-Amino-5-phosphonovalerate (D-APV), lidocaine or aCSF control. A total of 67 cells was recorded in 4 sessions. Of these, 58 cells exhibited stable firing patterns during the course of the session and thus could be considered for analysis. To assess the effect of the drugs on single unit firing in a resting state, we calculated mean firing rates over 30 second bins during perfusion intervals for each cell. Compared to aCSF perfusions, the perfusion of 0.5 mM NMDA induced a cessation of firing in 96% of neurons. Perfusion of 2% lidocaine blocked firing activity in 83% of cells. Finally, perfusion of 0.5 mM D-APV did not markedly modulate firing rates in any of the recorded cells but could block the mentioned NMDA effect. These findings confirm that this array can be used for time-specific local application of drugs during extracellular recordings in awake rats. Currently, the effect of D-APV perfusion on single unit and population activity during a 2-odour discrimination task is assessed. Pilot results confirm that OFC units exhibit differential firing patterns to cues predicting the appetitive and aversive outcome and show reward expectancy correlates. Results from drug perfusion in 2 rats performing this task will be presented.

KEY WORDS: OFC, microdialysis, D-APV, electrophysiology, reward prediction

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TITLE **β -ADRENOCEPTOR MEDIATED INHIBITION OF LONG-TERM ALCOHOL-RELATED MEMORY RECONSOLIDATION****AUTHORS**

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ABSTRACT

Well-consolidated fear-related memories, once retrieved, are vulnerable to disruption and require reconsolidation in order to be maintained. Recently, we provided evidence that reactivated reward-related memories are also susceptible to interference. Thus, using an instrumental conditioning paradigm we observed that propranolol (PROP), a β -adrenergic antagonist, reduced conditioned sucrose seeking, when injected immediately after reactivation of sucrose-related memories. In the current study we examine whether alcohol-related memories are also prone to disruption by PROP administration following their reactivation. In operant chambers male Wistar rats were trained to self-administer a 12% alcohol solution. After 3 weeks of abstinence the animals were re-exposed to the context and cues of the training chambers in a 20 minute retrieval session that was directly followed by a systemic injection of either PROP or saline. The rats were tested for cue-induced alcohol seeking behaviour on the consecutive day. The retrieval session, injection and test were repeated once every week for 2 weeks. PROP administration upon reactivation did not reduce alcohol seeking after the first reactivation test, however the second and third post-training tests showed a 30% reduction of alcohol seeking. Our data indicate that reconsolidation of alcohol-related memories can be disrupted after a long post-training interval and that β -adrenergic receptors may represent a novel target for pharmacotherapy of addictive behaviours, in particular in the context of cue-exposure therapies.

KEY WORDS: β -adrenoceptor, reconsolidation, alcohol, instrumental conditioning

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TITLE

BRAIN DEVELOPMENT AND BRAIN FUNCTIONING IN THE CLINICAL MANAGEMENT OF TRANSSEXUAL ADOLESCENTS

AUTHORS

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ABSTRACT

The clinical management of transsexual adolescents of the VUmc consists of suppression of puberty with GnRH analogues from the age of 12 and from pubertal stage 2 according to Tanner and of cross-sex hormones from the age of 16. The hypothesis of this study is that brain functioning and brain structure of transsexual teenagers treated with GnRH agonists is according healthy individuals without transsexuality. Therefore, we will investigate the consequences of long-term delay of puberty before, during and after treatment with Decapeptyl-CR® alone and in combination with cross-sex hormones in juvenile transsexuals by means of structural and functional MRI.

Little is known about aetiological aspects of transsexuality. Transsexuality is associated with atypical sex hormone levels during pregnancy. The group of transsexual adolescents of the VUmc is unique since these adolescents neither showed gender related behaviour corresponding with their biological sex, nor did they use cross-sex hormones, which might be influential on their brain development. We therefore believe that the best chances to find biological differences between transsexuals and non-transsexual are in this group. The hypothesis is that in transsexualism the development of brain structures and brain functioning is in the direction of the desired sex instead of the biological sex.

In this study we will focus on sex differences between transsexual adolescents and similar aged individuals of both sexes, as well as on possible determinants of the aetiology of transsexuality.

This study is an observational, cross-sectional (with longitudinal continuation) prospective follow-up study. 120 Male and female transsexual adolescents of 9-25 years old will be recruited. There will be 5 groups, in each group 12 MF and 12 FM transsexual patients will be included (1. ca 9-10 years, 2. ca 12 years, 3. 16 years, 4. 17 years and 5. 18-19 years). In addition 48 healthy subjects will be recruited, these will be one male and one female friend of each transsexual patient from group 2, 3 and 5.

We will measure total brain volume, amounts and percentages of gray and white matter and CSF, volumes of the frontal and temporal lobes and gyrfication. We will use voxel-based morphometry to examine human brain asymmetry and the effects of sex on brain structure. A region of interest approach will be adopted to investigate morphometric differences in brain regions because of the known sexual dimorphisms, these regions will be basal ganglia, amygdala, hippocampus, corpus callosum and hypothalamus.

Functional MR data will be acquired while subjects perform tasks likely to reflect differences in (sexually dimorphic) neuro-cognitive development, adjusted for age. These tests will inform us about brain function in transsexual patients throughout the different developmental phases (without and with treatment). Subjects will be offered three experimental conditions: a mental rotation task, a verbal task and an emotional task in random order.

Imaging includes a coronal 3D gradient-echo T1-weighted sequence (matrix 256 x 160, voxel size 1 x 1 x 1.5 mm, 160 sections) for structural MRI and echo planar imaging sequence (TR 2.3 s, TE 35 ms, matrix 96 x 96, field of view 192 x 192 mm) for functional MRI and will be performed on a Philips Intera 3.0 Tesla with a standard 8-channel head coil.

Psychometric data will be analyzed using a standard statistical package. Imaging data will be analyzed using SPM5.

KEY WORDS: Structural MRI, functional MRI, transsexuality, brain development, adolescents, Decapeptyl

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TITLE**SOCIAL DEFEAT AS AN ETHOLOGICAL MODEL FOR THE GENERATION OF DEPRESSION-LIKE SYMPTOMS IN MICE****AUTHORS**Jiun Youn, M.Verhage, O.Stiedl**DEPARTMENT/INSTITUTE**

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ABSTRACT

Depression is a psychiatric disorder that affects increasing numbers of people and is a serious concern for our society. Both genetic and environmental factors are expected to contribute to depression. However, both are poorly understood. Based on the beneficial effects of long-term treatment using “selective” serotonin reuptake inhibitors (SSRIs), the serotonergic system has been implicated to play a major role. However, the mechanism(s) how the beneficial effects of SSRIs are mediated have not been identified yet. The objective of the Ph.D. project is to establish the social defeat model in mice that allows investigating depression-like symptoms and its modulation. It is of particular importance to establish the behavior model in mice to exploit the advantages of genetic strategies. This will be eventually achieved by using mice with genetically modified serotonergic neurotransmission. As there is considerable comorbidity between anxiety and depression, screening of anxiety-like behavior will be used to select mouse models from recombinant inbred (BXD) strains with isogenic genes. Selected BXD strains, derived from mouse strains that exhibit low levels (C57BL/6J) and high levels of anxiety (DBA/2J), will be selected for subsequent tests using the depression model. This combination of methods in combination with the use of genetically modified mice will eventually allow to gain a better understanding of the role of serotonergic system in contributing to the vulnerability for depression-like disorders in an animal model, and to ultimately investigate the validity of results in the clinical setting.

KEY WORDS: Social stress, anxiety, depression, bullying, strain differences, social defeat, serotonin, 5-HT**TELEPHONE NUMBER:** 020- 5987089**E-MAIL-ADDRESS:** jiun.youn@cncr.vu.nl

TITLE**PROFILING ADHD USING LONGITUDINAL sMRI AND DTI: METHODS AND MEASURES****AUTHORS**Patrick de Zeeuw, Janna van Belle, Sarai van Dijk, Herman van Engeland, Sarah Durston**DEPARTMENT/INSTITUTE**

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is a common and impairing neuropsychiatric disorder of childhood, occurring in 3 to 5% of all school-age children (American Psychiatric Association, 1994). This disorder is associated with greater risks for low academic achievement, school dropouts, poor family and peer relations, aggression, substance abuse, driving accidents and chronic problems in adult adaptation (Barkley, 1990; Weiss & Hechtman, 1993). However, in a large number of children symptoms dissipate as they grow up and they go on to function normally and lead typical lives (Barkley, 1990; Weiss & Hechtman, 1993). This has led to speculation that ADHD may not so much represent a disruption, as a delay of brain development. The aim of this study is to address this issue.

There is a growing body of research supporting the existence of deficits in brain anatomy associated with ADHD, with evidence of reductions in overall brain size, cortical grey matter and subcortical structures (Durston, 2003; Seidman et al., 2005; Valera et al., 2006). However, reported effect sizes are small and results not always consistent. Typically, studies of brain anatomy in ADHD have included small, cross-sectional samples and have focused on volumetric measures of areas of theoretical interest. Such studies are easily confounded, as brain development is complex and associated with both progressive and regressive changes in brain anatomy. The first longitudinal studies of brain development in ADHD (Castellanos et al., 2001; 2002) have included large samples of subjects, but have largely considered volumetric measures. In this study, we will be combining longitudinal data from a large cohort of children and adolescents with state-of-the-art imaging methods (including DTI and Voxelbased Morphometry (VBM) and Cortical Thickness measures) to investigate brain development in ADHD. This will allow us to address the question whether ADHD represents a disruption or a delay of brain development. DNA will be acquired from children and their parents to allow for a preliminary investigation of the involvement of known ADHD risk genes in aberrant brain development in this disorder. Furthermore, we will acquire cognitive profiles of our participants in three neuropsychological domains: cognitive/inhibitory control, sensitivity to timing and sensitivity to reward and punishment. This poster presentation will introduce all these measures as well as our approach to combining these data.

KEY WORDS: ADHD, MRI, brain development, genetics, neuropsychology**TELEPHONE-NUMBER:** 030-2507084**E-MAIL-ADDRESS:** p.dezeeuw@umcutrecht.nl

TITLE**BEFORE PSYCHOSIS: A COMPARISON OF BRAIN VOLUMES IN ADOLESCENTS AT ULTRA HIGH RISK AND TYPICALLY DEVELOPING SUBJECTS****AUTHORS**

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ABSTRACT**Introduction**

An increasing body of evidence suggests that the onset of psychosis is preceded by well described, but non-specific prodromal symptoms that occur several years before the criteria of psychosis are met. Children and adolescents with these symptoms are therefore considered to be at Ultra High Risk for Psychosis (UHRP). In line with research supporting the existence of neuroanatomical abnormalities associated with established psychotic disorders, prodromal symptoms may reflect early pathological neurodevelopment in UHRP subjects. Identification of related neurobiological changes may therefore provide more insight into developmental aspects of psychosis, and as such further aid in the prediction and, ultimately, prevention of psychosis.

Methods

Structural MRI data of adolescent UHRP subjects (n=70) and healthy controls (n=61), matched for age, gender, hand preference and social economic status, has been gathered. MRI scans were acquired at baseline and are currently being acquired in a two year follow-up study. Volumetric analyses and Voxel Based Morphometry (VBM) approaches will be used to investigate differences between groups at baseline and over time. The poster presentation will include baseline volumetric data of our subject groups.

Hypotheses

Based on previous MRI studies, we hypothesize that the UHRP group will display global decreases in gray matter compared to healthy controls at baseline, and that these changes will be progressive over time.

KEYWORDS: Psychosis, prodrome, MRI, high risk

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TITLE**OLANZAPINE-INDUCED WEIGHT GAIN: AN ANIMAL MODEL USING MALE RATS****AUTHORS**Esther M. van der Zwaal, M.C.M. Luijendijk, S.E. la Fleur, R.A.H. Adan**DEPARTMENT/INSTITUTE**

Pharmacology and Anatomy, Rudolph Magnus Institute of Neuroscience, Utrecht

ABSTRACT

Olanzapine is a commonly prescribed antipsychotic drug that unfortunately often shows significant weight gain as a side effect. This weight gain can compromise patient compliance and is often accompanied by dyslipidemia and hyperglycemia, increasing the risk for diabetes and cardiovascular disease. The mechanisms responsible for this weight gain are not yet completely understood.

Olanzapine has affinity for dopamine, histamine, 5-HT, muscarinic and alpha-adrenergic receptors and gaining insight into which of these receptors are involved may be crucial to develop novel antipsychotics that are equally therapeutically effective but less prone to cause weight gain.

We are currently developing an animal model for olanzapine-induced weight gain using male Wistar rats to study in detail the effects on eating behaviour, food preference and locomotor activity. Because the half-life of olanzapine in male rats is only 2 ½ hours, compared to over 20 hours in humans, we decided to use osmotic minipumps to administer an olanzapine-solution continuously for 4 weeks in different paradigms. Retrospectively we identified problems concerning the long-term stability of olanzapine in solution. Nevertheless our preliminary results indicate a reduction of locomotor activity and an increase in food intake, meal size and duration as well as changes in diurnal feeding rhythm.

After having identified further the effects of olanzapine administration on different aspects of energy balance we plan to use this model to identify the receptors responsible for each of these effects. Similarly we plan to investigate the side effects of topiramate (an antiepileptic drug) which are the opposite of those of olanzapine, namely weight loss and improvement of glucose tolerance.

KEY WORDS: Antipsychotics, body weight, food intake, animal model, olanzapine, topiramate**TELEPHONE-NUMBER:** 030-2533113**E-MAIL-ADDRESS:** e.m.vanderzwaal@umcutrecht.nl

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