



15th PhD Annual Meeting

**Graduate School Neurosciences
Amsterdam Rotterdam**

&

**Rudolf Magnus Graduate School
of Neuroscience**

November 27 and 28, 2008

Woudschoten Conference Center, Zeist

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Cover: Nico Romeijn

Dear PhD student,

Welcome to the 15th Annual Meeting of PhD-students of the Graduate School Neurosciences Amsterdam and the Rudolf Magnus Graduate School of Neuroscience Utrecht at Conference Center Woudschoten in Zeist.

This year we would like to welcome the PhD students of the Department of Neuroscience Rotterdam to the annual meeting of the Amsterdam/Rotterdam (*ONWAR*) and Utrecht (*Rudolf Magnus*) Neuroscience Graduate Schools. 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 2rd 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 broad 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 Maarten Frens, who is board secretariat of the Neurofederatie and head of the research group "Cerebellar systems physiology" at the Department of Neuroscience in Rotterdam. 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 Rainer Goebel will give the Swammerdam Lecture on Thursday afternoon. Rainer Goebel is a full professor of Cognitive Neuroscience at the Psychology Department of the Maastricht University. His research interests include artificial neural networks of visual processing, neural correlates of attention, and structural and functional imaging of the human brain. He is a member of the board of governors of the F.C. Donders Centre for Cognitive Neuroimaging in Nijmegen and he is affiliated to the Netherlands Institute for Neuroscience in Amsterdam. It is a great honor to have him as a speaker at the 2008 PhD-student meeting.

The organizers also would like to thank the senior scientists from Rotterdam, Utrecht and Amsterdam for their willingness to come 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:

| | |
|---------------------------|--|
| Felisa van Hasselt | <i>Center for NeuroScience, SILS-UvA, Amsterdam</i> |
| Erika van Hell | <i>Neurology and Neurosurgery, UMCU, Utrecht</i> |
| Elly Hol | <i>Astrocyte Biology & Neurodegeneration, NIN, Amsterdam</i> |
| Els Møst | <i>Sleep and Cognition, NIN and VUmc, Amsterdam</i> |
| Jeroen Pasterkamp | <i>Neuroscience and Pharmacology, UMCU, Utrecht</i> |
| Evelien Platje | <i>Child- and Adolescent Psychiatry, VUmc, Amsterdam</i> |
| Marleen Sta | <i>Neurogenetics, AMC, Amsterdam</i> |
| Nelleke Verhave | <i>Diagnosis and Therapy, TNO Rijswijk, and VU, Amsterdam</i> |
| Jelte Wouda | <i>Anatomy and Neurosciences, VUmc, Amsterdam</i> |
| Nils Zuiderveen Borgesius | <i>Neuroscience, ErasmusMC, Rotterdam</i> |
| Esther van der Zwaal | <i>Neuroscience and Pharmacology, UMCU, Utrecht</i> |
| Els Borghols | <i>ONWAR, Amsterdam</i> |

09.00 - 09.50 Registration / coffee and tea

09.50 - 10.00 **Welcome** - Els Møst

Didactic comments -Ysbrand van der Werf

10.00 - 10.55 **Session 1: Brain Imaging** **chair: Dick Veltman**

Floris van Velden

Direct quantitative comparison of HRRT and HR+ scanners: an interscanner [11C]flumazenil test-retest study.

Nienke Dekker

Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia.

Jurgen Mourik

Effects of patient movement on the analysis of dynamic PET brain studies.

10.55 - 11.15 Printers market with coffee and tea

11.15 - 12.25 **Session 2: Electrophysiology and Visual Cortex** **chair: Freek Hoebeek**

Marijn van Wingerden

Single unit and network coding of orbitofrontal cortex neurons during a 2-odour discrimination task.

Silviu Rusu

Cellular mechanisms underlying complex extracellular waveforms from the Calyx of Held synapse.

Duco Endeman

Cones perform a nonlinear transformation on a natural time series of intensities.

Hadi Saiepour

Role of β -catenin in functional and structural plasticity of the visual cortex.

12.25 - 13.30 Lunch and printers market

13.30 - 14.00 **Blitz Session I** **chair: Ysbrand van der Werf**

14.00 - 15.30 **Poster Session/** Printers market

15.30 - 16.00 Printers market

16.00 - 17:10 **Session 3: Phenotyping and Biorhythm** **chair: Oliver Stiedl**

Alexander Cupido

Detecting cerebellar phenotypes with the Erasmus Ladder.

Annetrude de Mooij-van Malsen

Behavioural genetics of avoidance: a mouse phenotype linked to a human mood disorder.

Els Møst

Skin temperature rhythms in Alzheimer's Disease and cognitive impaired elderly.

Ellen Hessel

Mapping quantitative trait loci for febrile seizure.

17:10 - 17.30 Coffee and tea

17.30 - 18.40 **Swammerdam Lecture by prof dr. Rainer Goebel** **chair: Felisa van Hasselt**

Using the BOLD Signal for communication and neurofeedback: automatic decoding of real-time fMRI data.

18.45 - 20.30 Dinner

20.30 - 21.30 Science Quiz

08.30 - 09.30 Breakfast

Didactic comments - Wiep Scheper

09.30 - 09.35 **Introduction** - Jelte Wouda

09.35 - 10.45 **Session 4: Age and Neurodevelopment** **chair: Jeroen Pasterkamp**

Jinte Middeldorp

GFAP δ expression in neurogenic astrocytes in the developing and adult brain.

Nils Zuiderveen Borgesius

Accumulated DNA damage causes age-related cognitive decline.

Charlotte Oomen

Sex-dependent effects of early life stress on the hippocampus.

Max Schlager

Madmax coordinates exocytotic Rab6 vesicle transport and regulates neuronal development.

10.45 - 11.00 Coffee and tea

11.00 - 11.45 **Blitz Session II** **chair: Wiep Scheper**

11.45 - 13.00 Lunch

13.00 - 14.45 **Poster Session II**

14.45 - 15.55 **Session 5: Neurodegeneration and protection** **chair: Paul Lucassen**

Elly Vereyken

Alternatively and classically activated macrophages vary in migratory capacity and migrate differently in organotypic CNS cultures.

Gijs Kooij

P-glycoprotein is a novel immunomodulator in multiple sclerosis.

Marcel Raspe

Mimicking proteasomal release of polyglutamine peptides using a novel cell-based tool

Judith Gillis

Aggregation of expanded, pure polyglutamine peptides can be inhibited by overexpression of the chaperones DnaJB6 and DnaJB8

15.55 - 16.10 **Announcement FENS Forum 2010** - Maarten Frens

16.10 - 16.20 **Poster Award** - Maarten Frens, Nelleke Verhave, Erika van Hell, Harold Mac Gillavry

16.20 - 16.30 **Blitz and Oral Presentation Award** - Retreat committee 2008

16.30 - 16.40 **Closing remarks** - Jelte Wouda

Blitz Session I

November 27, 13.30 - 14.00

chair: Ysbrand van der Werf

Nico Romeijn
Rana Al Hussainy
Dianne van den Heuvel
Esther van der Zwaal
Felisa van Hasselt
Femke Wouters
Hemi Malkki
Inge van Soelen
Jean-Pierre Sommeijer
Nelleke Verhave
Margreet Ridder
Mette Somers
Nutabi Camargo
Priyanka Rao
Sebastian Schagen
Simone van den Berge

Blitz Session II

November 28, 11.00 - 11.45

chair: Wiep Scheper

Anne Kan
Hans Buiten
Hayriye Cagnan
Jelte Wouda
Joanna Korecka
Jurjen Broeke
Kasper Roet
Kelly Diederer
Laura Smit-Rigter
Marieke de Boer
Marjolijn Mertz
Marleen Sta
Martijn Wokke
Liesbeth Bijlsma
Marek Brandys
Danielle Counotte
Ruben van Doorn
Teresa Alves dos Santos
Cathalijn Leenaars
Willem Huijbers

Group A

Chair: Freek Hoebeek

- 7) Nico Romeijn
Skin temperature as a predictor for lapses in vigilance.
- 8) Rana Al Hussainy
Synthesis of ¹⁸F-labelled cubyl-WAY.
- 9) Rebecca Schutte
Fast and slow spindles relate inversely to motor skills in primary school aged children.
- 10) Rhea van de Bospoort
Identifying molecular mechanisms underlying secretory vesicle release in neurons.
- 11) Ria de Haas
Automated detection of compulsive checking behaviour in rats.
- 12) Rogier Poorthuis
Modulation of synaptic inputs to layer II/III pyramidal neurons in the prefrontal cortex by nicotine.

Group B

Chair: Ysbrand van der Werf

- 13) Diana Nijholt
ER stress is associated with phosphorylation of tau in the pathology of Alzheimer's disease and Pick's Disease.
- 14) Dianne van den Heuvel
Study to elucidate Neogenin signalling and its role in axon guidance.
- 15) Eelke Snoeren
Female sexual behavior and pharmacology in serotonin transporter (SERT) knockout rats.
- 16) Elemi Breetvelt
Specificity of risk factor for psychotic symptoms in the general population; ethnicity the odd one out?
- 17) Elisa Hoekstra
Identifying the specific role of transcription factors Lmx1a and Lmx1b in the genetic cascade leading to mesodiencephalic dopaminergic neurons.
- 18) Esther van der Zwaal
Drug-induced weight gain: effects of olanzapine in an animal model.

Group C

Chair: Elly Hol

- 19) Eva Blaas
High-content screening of gene candidates for Parkinson's disease.
- 20) Evelien Platje
The cortisol awakening response in disruptive behavior disorder compared to normal children.
- 21) Evert-Jan Kooi
Abundant extracellular myelin in the meninges of patients with multiple sclerosis.
- 22) Felisa van Hasselt
Maternal care influences function and morphology in the adult rat hippocampus in a sex-dependent manner.
- 23) Femke Wouters
Brain activation during mental rotation in transsexual adolescents: an fMRI study.
- 24) Fleur Zeldenrust
Inhibitory structures in the hippocampus.

Group D

Chair: Jeroen Pasterkamp

- 31) Hemi Malkki
Correlations between operant learning performance and quantitative trait loci in recombinant inbred mice.
- 32) Henrique Cabral
Hippocampal coding of routes and sequences on the Sarmaze in wild-type and CA1 NR-1 KO mice
- 33) Inge van Soelen
The relation between attainment of motor milestones and volumetric brain measures in healthy 9-year old twins.
- 34) Jacobine Buizer-Voskamp
Recurrent CNVs disrupt three candidate genes in schizophrenia patients.

- 35) Jasper Poort
The role of attention in figure-ground segregation.
- 36) Jean-Pierre Sommeijer
The GABA_AR subunit $\alpha 1$ is involved in but not essential for ocular dominance plasticity.

Group E

Chair: Oliver Stiedl

- 43) John Silvio Soria van Hoeve
Dynamic development of the Calyx of Held.
- 44) Jolanda Prins
Triple reuptake inhibitors: behavioral and microdialysis studies in the olfactory bulbectomy model of depression.
- 45) Joost Wiskerke
Differential effects of the CB1 receptor antagonist SR141716A and the FAAH-inhibitor URB597 in the 5-choice serial reaction time task.
- 46) Jornt de Gruijl
Anticipatory grip force control using a cerebellar model
- 47) Jorrit van Asselt
Electrophysiological characterization of Connexin 55.5. and Connexin 52.6.
- 48) Juliane Lauks
Subcellular localisation of Neurobeachin.

Group F

Chair: Sabine Spijker

- 55) Myrre van Spronsen
TRAK proteins regulate trafficking of mitochondria in neurons.
- 56) Natalia Goriounova
From behavior to AMPA receptors and back: neuroadaptive changes in the rat prefrontal cortex implicated in vulnerability to relapse to heroin seeking.
- 57) Natasha Pasricha
The physiological role of membrane MRs in hippocampal function.
- 58) Nelleke Verhave
Riluzole treatment in the marmoset MPTP model.
- 59) Qiluan Schaafsma-Zhao
Endocannabinoid signalling in the prefrontal cortex.
- 60) Margreet Ridder
MLC1 mutations cause dysfunction of chloride channel activity, a disturbance of volume regulation, and cerebral White Matter Edema.

Group G

Chair: Ronald van Kesteren

- 67) Marek Brandys
Genotypes and phenotypes in Anorexia Nervosa.
- 68) Matthijs Bossong
Delta9-tetrahydrocannabinol induces dopamine release in the human striatum.
- 69) Metten Somers
The use of Functional Transcranial Doppler ultrasound for the assessment of language lateralization. A comparison with functional MRI.
- 70) Mike Marlatt
Coordinated evaluation of gliosis in the Alzheimer hippocampus through immunohistochemistry.
- 71) Nutabi Camargo
Deletion of SCAP in astrocytes: the implication of disrupted lipid metabolism in the mouse brain.
- 72) Laurens Witter
A look inside cerebellar cortical neurons: linking electrophysiology to morphology.

Group H

Chair: Alwin Derijck

- 79) Oswald Bloemen
Psychosis and autism. An in vivo magnetic resonance imaging study of brain anatomy.
- 80) Patricia Klemmer
Quantitative synaptic proteomics in a mouse model for the Fragile X Syndrome reveals molecular changes underlying neurotransmission and synapse morphology.

- 81) Pieter Goltstein
Plasticity and functional micro-organization of cross-modal interactions in the mouse visual cortex.
- 82) Pieter van Bokhoven
Social defeat stress and subsequent antidepressant or behavioral therapy.
- 83) Priyanka Rao
Quantitative proteomics of memory consolidation in two inbred mouse strains.
- 104) Christiaan Stronks
Electro-acoustic stimulation in the cochlea of partially deafened guinea pigs.

Group I

Chair: Susanne la Fleur

- 91) Rubén Saavedra
Olfactory Ensheathing Glia and the regeneration of the olfactory system: involvement of phagocytosis, cholesterol recycling and modulation of the extracellular matrix.
- 92) Sandra van der Salm
Normal cortical excitability yet polyphasic MEP's in myoclonus dystonia - a TMS study.
- 93) Sebastian Schagen
Voxel Based Morphometry of the transsexual adolescent brain.
- 94) Simone van den Berge
Neurogenic astrocytes in the adult human brain have a specialized intermediate filament network.
- 95) Simone de Jong
Relating gene expression network results to behavioral phenotypes in a chromosome substitution strain F2 population in order to identify a gene underlying a QTL.
- 96) Simon-Shlomo Poil
Avalanche dynamics of ongoing oscillations in vitro, in vivo and in computational models

Poster Session II

November 28, 13.00 - 14.45

Group J

Chair: Elly Hol

- 1) Aleksandra Badura
Inhibition in the cerebellar cortex – the role of interneurons in motor learning.
- 2) Anne Kan
Epileptogenic changes in a juvenile model of temporal lobe epilepsy.
- 3) Antoin de Weijer
Subregions in the frontal eye fields projecting to the superior colliculus are crucial in making anti-saccades: an fMRI-DTI study.
- 4) Aram Hossaini
The role of ARC expression in the spinal cord.
- 5) Arthur de Jong
Visualizing synaptic heterogeneity in autaptic neurons.
- 6) Asiya Giniatullina
Specific interaction of the priming factor DOC2B with PIP₂.

Group K

Chair: Jeroen Pasterkamp

- 25) Floris Klumpers
Method development studies for repeatedly measuring anxiolytic drug effects in healthy humans.
- 26) Frank Meye
New concepts in G-Protein coupled receptor signalling in the mesolimbic dopamine system.
- 27) Hannemieke van der Lei
The relationship between genotype and phenotype in Vanishing White Matter: the influence of the second mutation.
- 28) Hans Buiter
A putative radiolabeled ligand for in vivo imaging of the M1 muscarinic acetylcholine receptor by PET.
- 29) Hans-Rüdiger Geis
Intracellular mechanisms underlying rate and temporal tuning to sinusoidal amplitude modulated tones in the mouse inferior colliculus.

- 30) Hayriye Cagnan
Thalamic network response to oscillatory activity associated with Parkinson's disease and deep brain stimulation.

Group L

Chair: Wiep Scheper

- 37) Jelte Wouda
Operant alcohol self-administration and five-choice reaction time task performance in Wistar rats exposed to chronic alcohol during adolescence.
- 38) Jeroen van Zanten
Stimulated gene expression profiles as a blood marker in antidepressant-naïve major depressed patients.
- 39) Jeroen Melief
Severe multiple sclerosis is associated with low stress-axis activity.
- 40) Ji Un Youn
Strain differences in passive avoidance extinction in mice.
- 41) Joanna Korecka
Selecting and validating gene targets implicated in parkinson's disease development and progression.
- 42) Jochem Cornelis
Identification and functional characterization of novel repressors of neuronal regeneration.

Group M

Chair: Christian Lohmann

- 49) Julia Meijer
The neuroanatomy of semantic verbal fluency deficits: implications for prediction.
- 50) Jurjen Broeke
Vesicle release supports but is not essential for directed outgrowth.
- 51) Kasper Roet
The applicability of bioluminescence to measure cell survival after implantation in rat spinal cord.
- 52) Katja Ritz
Myoclonus-Dystonia: clinical and genetic evaluation of a large cohort.
- 53) Kerstin Wirz
Characterizing the function of Neuropilin 1 and 2 in the interaction between meningeal and Schwann cells.
- 54) Laura Smit-Rigter
Specific deficits in social interaction in mice lacking the 5-HT_{3A} receptor.

Group N

Chair: Harm Krugers

- 61) Marieke de Boer
Flexibility of behavioural planning in mouse prefrontal cortex.
- 62) Marjan Steenweg
L-2-Hydroxyglutaric Aciduria: pattern of MRI abnormalities in 53 patients.
- 63) Marjolijn Mertz
Calcium transients in PFC axons mediated by nicotinic activation: effects of axonal Type III Nrg1 signaling.
- 64) Marleen Sta
Innate and adaptive immunity in amyotrophic lateral sclerosis (ALS): evidence of complement activation.
- 65) Marloes Joosen
Therapeutic efficacy of physostigmine and obidoxime in a soman-poisoned guinea pig model.
- 66) Martijn Wokke
Up and down with TMS and EEG: Discriminating disruption of figure ground segregation signals in early visual areas.

Group O

Chair: Louk Vanderschuren

- 73) Kelly Diederer
Brain activation preceding the experience of auditory verbal hallucinations.
- 74) Liesbeth Bijlsma
Differential role for basolateral amygdala and prefrontal cortex in CRF-induced alterations in startle reactivity.

- 75) Linda Holtman
How complement protein C6 deficiency affects epileptogenesis.
- 76) Linda Schoo
Ranking your cognition.
- 77) Ling Shan
Stable histamine production in spite of extensive Parkinson pathology in the Hypothalamic Tuberomamillary nucleus.
- 78) Maarten Witte
Mitochondrial alterations in MS lesions.

Group P

Chair: Paul Lucassen

- 84) Cathalijn Leenaars
Sleep promotes instrumental learning in rats.
- 85) Cathrin Canto
A comparison of neurons within the medial-, and lateral entorhinal cortex.
- 86) Chris Schubart
Initial age of cannabis use and the risk of psychotic symptoms.
- 87) Cleo Crunelle
Innovative approaches for cocaine pharmacotherapy: the case of rimonabant.
- 88) Danielle Counotte
Synaptic proteomics of rat prefrontal cortex affected by adolescent nicotine exposure.
- 89) Danielle van Versendaal
Measuring the effects of environmental enrichment on visual plasticity of adult mice by in vivo calcium imaging.
- 90) Ruben van Doorn
The sphingolipid rheostat influences brain endothelial integrity.

Group Q

Chair: Anne-Marie van Dam

- 97) Teresa Alves dos Santos
Do Pitx3 and En1 interact in the mesodiencephalic dopaminergic (mdDA) system?
- 98) Thaís Rizzi
Replication of candidate genes, locus-wide association study for IQ.
- 99) Tony Cijssouw
Lifetime at the membrane: the molecular factors that influence tethering and docking of secretory vesicles at their target.
- 100) Willem Huijbers
Dissociating the “retrieval success” regions of the brain: effects of retrieval delay.
- 101) Xin Qiao
Anti-epileptic drug interactions with α -subunits of voltage-gated Na^+ channels stably expressed in HEK293 cells.
- 102) Yael Reijmer
Cognitive decline in type 2 diabetes mellitus: a longitudinal population-based study.
- 103) Yasmin Namavar
tRNA splicing endonuclease mutations cause pontocerebellar hypoplasie.

FENS Forum 2010

Call for Student Party in the Melkweg Amsterdam

The next FENS Forum of European Neuroscience will be held in the RAI Convention Center Amsterdam, from 3-7 July 2010. This biennial meeting is growing in quality and number of participants and is nowadays a must for all European neuroscientists. Next to a series of up-to-date parallel symposia and of keynote lectures, morning and afternoon poster sessions are the backbone for scientific exchange at the meeting. You are all invited to visit the website <http://forum.fens.org/2010> for information. The scientific program will be available mid 2009, and registration will be open as of December 2009. If you are a member of the Dutch Neurofederation (free membership at <http://www.neurofederatie.nl>), you get a discount on your entrance fee.

The FENS Forum in Amsterdam is the ideal opportunity to present your work. In fact it is the chance for Dutch neuroscience to show up and expose what is going on in the various centers of brain research. The Dutch Neurofederation acts as a host for the European neuroscientists, and wishes to promote wide attendance of Dutch neuroscientists. The local organizing committee appointed by the Neurofederation would like to make the meeting not only a scientific success but also socially. One of the main social events will be a Student Party in "De Melkweg" on Monday 5 July 2010. The local organizers have decided to form a student group that will be in charge of organizing this party. The intentions are to have the early evening filled with various parallel (Dutch) cultural activities, possibly ranging from ballet to stand-up comedy, and from music to movie, etc. in all halls of "De Melkweg", followed by a big party.

If you have experience with organizing such parties and think that you can contribute, you are welcome to let us know your interest. The present group of students still needs enforcements, especially with someone who can make a website for the purpose of student exchange. Contact Prof.dr. Maarten Frens (m.frens@erasmusmc.nl) of the local organizing committee if you can contribute to make the Student Party a never-to-forget Forum 2010 event.

Gerard Boer
(chair local organizing committee)

SWAMMERDAM LECTURE

TITLE

USING THE BOLD SIGNAL FOR COMMUNICATION AND NEUROFEEDBACK: AUTOMATIC DECODING OF REAL-TIME FMRI DATA

AUTHOR

Rainer Goebel

DEPARTMENT/INSTITUTE

Dept. of Neurocognition, Faculty of Psychology, Maastricht University, Maastricht

ABSTRACT

Several medical conditions (e.g., brain injury, stroke, progressive neurological diseases) can lead to complete paralysis while largely preserving sensory and cognitive functions and associated brain activation. We investigated whether healthy subjects are able to "write" solely on the basis of voluntary control of the fMRI (BOLD) signal. Using a guided display technique, we show that subjects can learn in less than half an hour to produce reliably any letter of the alphabet in a single trial. To achieve this performance, subjects use three mental strategies to modulate spatio-temporal properties of the fMRI signal in three different brain areas. While the transmitted information (BOLD time courses from regions-of-interest) has been initially decoded offline by human raters, we have recently implemented a fully automatized real-time "brain reading" technique.

The developed paradigm and decoding technique might be applied in locked-in patients to let them communicate their wishes and thoughts without extensive pre-training.

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TITLE

DIRECT QUANTITATIVE COMPARISON OF HRRT AND HR+ SCANNERS: AN INTERSCANNER [¹¹C]FLUMAZENIL TEST-RETEST STUDY

AUTHORS

Floris H.P. van Velden^{*}, Reina W. Kloet, Bart N.M. van Berckel, Fred L. Buijs, Gert J. Luurtsema, Adriaan A. Lammertsma, Ronald Boellaard

DEPARTMENT/INSTITUTE

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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. The purpose of this study was (1) to directly compare quantitative accuracy of the HRRT relative that of a clinical (whole body) HR+ PET scanner (CTI/Siemens, Knoxville, TN, USA) and (2) to assess the effects of differences in spatial resolution between both scanners (~2.7 mm and 6 mm for HRRT and HR+, respectively). This assessment was performed by paired [¹¹C]flumazenil brain scans in 7 healthy volunteers, i.e. for each volunteer scans (including arterial sampling) were acquired on both scanners on the same day, thereby minimizing intersubject variability.

Parametric volume of distribution (V_T) were generated using Logan plot analysis. In addition, a basis function method (BFM) implementation of a single tissue compartment model was used to generate parametric V_T . Logan V_T analysis of HRRT data (figure 1) showed higher values than for HR+ data (linear regression slope with intercept fixed at origin of 1.16 to 1.19, depending on the HRRT reconstruction method used). Smoothing HRRT reconstructions with a 6 mm full width at half maximum Gaussian kernel reduced this slope to values near the line of identity (1.05 to 1.07), retaining good correlation between HR+ and HRRT data (Pearson's correlation coefficient r of 0.95 to 0.98). Similar trends were observed for BFM V_T , where the slopes with intercept fixed at origin improved from 1.14-1.28 to 1.00-1.03 (with r of 0.80-0.88). This illustrates that, by matching resolution of HRRT and HR+, hardly any differences can be observed between both scanners. Therefore, the higher values of pharmacokinetic parameters values obtained from unsmoothed HRRT data can be attributed entirely to a reduction of partial volume effects.

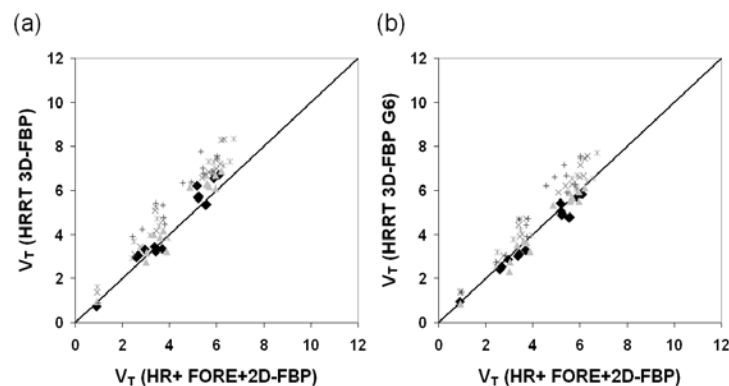


Fig 1. Correlation between parametric human [¹¹C]flumazenil Logan V_T obtained with various HRRT reconstruction methods against corresponding Logan V_T obtained with HR+ 2D-FBP+FORE: (a) 3D-FBP, (b) 3D-FBP smoothed with 6 mm full width at half maximum Gaussian kernel.

This work was financially supported by the Netherlands Organisation for Scientific Research (NWO, VIDI Grant 016.066.309).

KEY WORDS: High-Resolution Research Tomograph, HR+, brain imaging, quantitative comparison, parametric imaging

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TITLE**CANNABIS USE AND CALLOSAL WHITE MATTER STRUCTURE AND INTEGRITY IN RECENT-ONSET SCHIZOPHRENIA****AUTHORS**

Nienke Dekker, Nicole Schmitz, Bart D. Peters, Therese A. van Amelsvoort, Don H. Linszen, Lieuwe de Haan

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ABSTRACT

Adolescent-onset cannabis use, compared to later use, has been associated with a higher risk for developing symptoms of schizophrenia. Although cannabis use has been associated with brain structure abnormalities in patients with schizophrenia, the effect of the onset age of cannabis use on brain structure has not yet been studied in individuals with schizophrenia. To test the hypothesis that early (adolescent)-onset of cannabis use in male schizophrenia patients is associated with abnormalities in white matter structure and integrity, we used high resolution structural and diffusion-tensor brain images to compare three groups of patients: those who started regular use of cannabis (1) before the age of 15 years (early-onset cannabis users, n=10), (2) at the age of 17 years or later (late-onset cannabis users, n=8), and (3) those who were cannabis naïve (n=8). Cannabis naïve patients showed reduced white matter density and reduced fractional anisotropy (a measure of white matter integrity) in the splenium of the corpus callosum, compared to patients with early-onset cannabis use. Our results suggest that the age of onset of cannabis use is not identifying for white matter abnormalities in schizophrenia patients, however, our results might also indicate a more vulnerable brain structure in cannabis naïve schizophrenia patients. We are now in the process of comparing fractional anisotropy between healthy controls and the patient groups. Results will be presented at the annual meeting.

KEY WORDS

Schizophrenia; cannabis use; fractional anisotropy; diffusion tensor imaging; structural magnetic resonance imaging; white matter

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TITLE
EFFECTS OF PATIENT MOVEMENT ON THE ANALYSIS OF DYNAMIC PET BRAIN STUDIES

AUTHORS

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ABSTRACT

Introduction. Positron emission tomography (PET) is a medical imaging technique that is used to study tissue function *in vivo* by imaging and measuring regional tracer concentrations of radiopharmaceuticals labelled with a positron emitter. A regular PET scan last at least 60 min, in which patient motion could occur. A large part of all subjects who are included in PET studies suffer from the Alzheimer disease, Parkinson disease or have a traumatic injury for which it is even harder to lay still. Patient motion may hamper the outcome of a PET study. First of all, patient motion during the PET scan may reduce the spatial resolution [1]. Furthermore, patient motion may alter the time activity curve (TAC) measured on a set of region of interests and hence impact on the outcome of tracer kinetic analysis. The purpose of this study was to evaluate what the effect of patient movement is on the analysis of dynamic PET brain studies.

Materials and Methods. A simulated dynamic PET scan with high cortical uptake was created. Two types of motion was added to the simulated PET scan. First of all, different rotations (3°, 4°, 5° and 6°, see Fig. 1 top row) were applied, simulating the napping effect at the end of a scan. These rotational movements correspond to a movement of approximately 6.8, 8.2, 9.6 and 11 mm respectively. The second type of motion simulates an axial movement (2, 4, 6, 10 and 20 mm, see Fig. 1 bottom row) of a subject. This movement may occur when a subject moves out of the scanner. For the analysis, TAC and Logan volume of distribution (V_T) parametric images were calculated. TAC and mean Logan V_T values for different anatomic regions were calculated and compared to the original values.

Results. Differences in TAC values up to 98% were found (parietal lobe) when an axial motion of 20 mm was applied. Largest differences between original TACs and TACs with motion were found in the pre-frontal lobe (2-30%), thalamus (1-52%), parietal lobe (7-98%) and putamen (9-34%). For the same regions, lower Logan V_T values were found (up to 45% for the parietal lobe).

Conclusion. This study shows that the effect of patient motion on TAC and the outcome of tracer kinetic are large, especially for larger movements. However, even if only small motion is present, differences in TAC for small anatomic regions is still considerable. Therefore, to obtain accurate results, it is necessary for the analysis of dynamic PET brain studies to inspect and correct the data for motion.

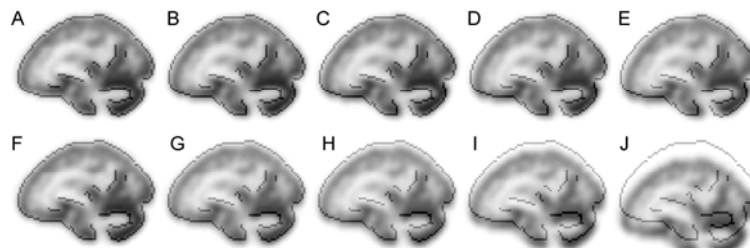


Fig. 1 – Different kind of motion was added to the original simulated PET images (A). The top row (B)-(E) showed a rotational movement of 3 to 6° and the lower row (F)-(J) an axial translational movement of 2, 4, 6 10 and 20 mm, respectively. The light grey contour on top of each image represents the unmoved image.

References

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Acknowledgement

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KEYWORDS

Positron Emission Tomography, PET, brain imaging, motion correction

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TITLE
**SINGLE UNIT AND NETWORK CODING OF ORBITOFRONTAL CORTEX NEURONS DURING A 2-
ODOUR DISCRIMINATION TASK**

AUTHOR(S)

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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 temporal organisation of this reward-related information has not yet been investigated in detail.

We recorded activity from OFC neurons in 3 awake male Wistar rats during a 2-odor go/no-go discrimination task using an electrode array holding 14 independently moveable tetrodes. We recorded 525 cells in 17 sessions where the rats attained a behavioral criterion of 90% correct performance over a 30 trial moving block. 467 cells had more than 500 detected spikes and were included in further analysis. We found $30\% \pm 5.8\%$ of cells with significantly modulated firing rate in the delay period when the rat was waiting for reinforcer delivery compared to baseline spiking activity, comparable to numbers found in previous studies.

On the network level, we found significant clustering of unit activity in relation to events in the behavioral task that was also expressed in a network parameter. This organization could help in the transfer of motivational information from 'limbic' areas to areas with direct motor output connections to influence overt behavior.

will be presented.

KEY WORDS:

OFC, electrophysiology, reward prediction, network analysis

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TITLE**CELLULAR MECHANISMS UNDERLYING COMPLEX EXTRACELLULAR WAVEFORMS FROM THE CALYX OF HELD SYNAPSE****AUTHORS**

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ABSTRACT

The calyx of Held synapse is a giant axosomatic synapse between the globular bushy cells of the anteroventral cochlear nucleus and the principal cells of the medial nucleus of the trapezoid body. Because of its accessibility, this synapse has been used extensively to study presynaptic release mechanisms or mechanisms of short-term plasticity in slice recordings. However, the significance of these findings for auditory signaling is still unclear. During in vivo recordings, transmission across this synapse is characterized by the presence of a complex extracellular waveform, consisting of both a pre- and a postsynaptic component, with quite variable shapes. To study the cellular mechanisms underlying these complex extracellular waveforms, we performed simultaneous postsynaptic whole cell and extracellular recordings at the calyx of Held synapse in acute brainstem slices from adult mice. We deconstructed different components of the extracellular waveforms by comparing intra- and extracellular signals during intracellular voltage steps, current steps and orthodromically evoked excitatory postsynaptic currents and potentials. We will present experimental and modeling data that the measured complex extracellular waveforms result from both capacitive and resistive currents and that well-isolated extracellular recordings from the calyx of Held synapse can be used to estimate essential steps of the signal transduction across this synapse.

KEY WORDS

Waveforms, MNTB, Synaptic transmission

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

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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 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 have examined 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.

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

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**ROLE OF β -CATENIN IN FUNCTIONAL AND STRUCTURAL PLASTICITY OF THE VISUAL CORTEX****AUTHORS**

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ABSTRACT

As a part of Wnt signaling pathway, β -catenin activates the TCF/LEF transcription factors. Also its complex with cadherin regulates neuronal adhesion, which leads to regulating total axonal and dendritic length and arborization. There is a correlation between β -catenin levels and total dendritic branch tip number. Sequestering β -catenin decreases dendritic arborization. β -catenin also binds to actin cytoskeleton through α -catenin and helps some steps of presynaptic assembly through binding to some of PDZ elements. It has a role in localizing synaptic vesicles at the presynaptic active zone. Altogether, β -catenin may be a key player in regulating spine morphology and synaptic plasticity. The Cre-lox recombination system is used to produce mice in which β -catenin gene is knocked out in a temporally and spatially restricted fashion. Crossing β -catenin loxP mice with a Cre expressing line with a broad expression, causes excision of exons 2-6, thereby knocking out β -catenin gene in most pyramidal neurons of the visual cortex. Intrinsic optical imaging showed that β -catenin knockouts have a lower acuity compared to controls. Since Cre expression is only in the cortex and not in retina or thalamus, a set of functional and structural approaches were used to reveal the underlying changes in cortices of β -catenin knockout mice.

KEY WORDS

β -catenin, synaptic plasticity, visual cortex

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TITLE**DETECTING CEREBELLAR PHENOTYPES WITH THE ERASMUS LADDER****AUTHORS**Alexander Cupido, S.K.E. Koekkoek, C.I. de Zeeuw**DEPARTMENT/INSTITUTE**

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ABSTRACT

Behavioral phenotyping of mutant mice is of considerable interest in neuroscience. The cerebellum is a frequently studied part of the brain with regard to motor behavior. A number of behavioral assays are available that can be used to test cerebellar motor behavior. At one side are the non-invasive, high throughput assays (e.g. accelerating rotarod), on the other hand are the more invasive tasks (e.g. eye blink conditioning), where surgery has to be done and the recording is done with an elaborated system. Logically the throughput of this type of assay is much lower, and the costs are much higher but the outcome is often more satisfying in that it tells the researcher in much more detail what exactly the phenotype of the mutant mouse is.

I will introduce a novel assay that in our view combines the benefits of the low and high throughput types of cerebellar tasks: the Erasmus Ladder. It is a non-invasive, fully automated, medium throughput task where motor behavior can be assessed in great detail. This will be demonstrated by the analysis of several mouse models.

KEY WORDS

Mice, phenotyping, motor behavior, cerebellum, Erasmus Ladder

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TITLE**BEHAVIOURAL GENETICS OF AVOIDANCE; A MOUSE PHENOTYPE LINKED TO A HUMAN MOOD DISORDER****AUTHORS**

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ABSTRACT

Mood disorders have a powerful effect on the lives of many people. Finding mechanisms underlying these disorders is essential to develop selective treatment. Corresponding translational research is still inadequate at various levels. The identification of susceptibility genes for psychiatric endophenotypes across species may provide a new step forward to unravel the complex genetics of relevant neurobehavioural disorders. Therefore, to increase behavioural resolution, we developed an automated home cage environment, assessing the animals' reduced preference for exposed areas (avoidance behaviour) independent of motor activity levels. To efficiently screen for novel genetic loci, we used chromosome substitution strains of mice derived from C57BL/6J (host) and A/J (donor) strains. This way, individual chromosomes that contribute to the behavioural trait can be rapidly identified. Following behavioural testing of the panel of 21 chromosome substitution strains in the home cage environment, we identified different chromosomes regulating either motor activity levels or sheltering preference. Further genetic fine mapping revealed a Quantitative Trait Locus (QTL) for baseline avoidance in mice, syntenic with a human genetic linkage region for bipolar disorder. By combining mouse sequence data with data from the WTCCC GWA study, we identified 3 candidate genes with significant allele frequency differences between 2,938 healthy controls and 1,868 bipolar patients. These findings pave new roads to identify novel mechanisms underlying bipolar disorder endophenotypes and to provide genetic validity for translational research of these endophenotypes. To further confirm the validity and function of these candidate genes, expression patterns and physiological function are currently being examined.

KEY WORDS

Psychiatric disorders; chromosome substitution strains; animal model; Quantitative Trait Loci; home cage environment

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TITLE
SKIN TEMPERATURE RHYTHMS IN ALZHEIMER'S DISEASE AND COGNITIVE IMPAIRED ELDERLY

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ABSTRACT

With aging and even more so in neurodegenerative disease, the circadian rhythm of core temperature may show changes, such as a decreased amplitude. Changes occur as well in the regulation of skin temperature. Compared to younger adults, elderly people show attenuated skin blood flow responses to heat and cold and a lower maximal skin vasodilatation, regardless of gender and fitness. It has not been investigated previously how the diurnal profile in skin temperature changes with age and neurodegenerative disease. The aim of the present study was to elucidate this, as well as to investigate whether possible alterations in nocturnal and daytime skin temperature might be related to alterations in, respectively, sleep quality (Brain 2008;131:500-513) and cognitive performance (Sleep 2007;30:96-103).

Using iButtons skin temperature (Ts) was monitored unobtrusively at home for 24 hours in elderly people with different levels of cognitive decline; Subjective Memory Complaints (SMC), Mild Cognitive Impairment (MCI), presenile Alzheimer (presAD), Alzheimer Dementia (AD) and healthy, age matched controls. Activity was assessed with actigraphy. Lights out and get up time were measured with a pressure pad, put on the mattress, connected to a logger equipped with a light sensor. ANOVA was used to evaluate group differences in the average daytime and night time proximal (Ts_{proximal}) and distal (Ts_{distal}) skin temperatures.

Only during daytime, all cognitively impaired groups maintained a higher Ts than controls. Group differences reached significance on Ts_{proximal} for AD (p=0.001), for presAD (p=0.010 and for MCI (p=0.008), all versus controls. Differences could not be explained by activity levels or ambient temperature. The data suggest that the sympathetic vasoconstrictive response of the skin vasculature to an upright position is compromised in cognitively impaired elderly. An increased skin temperature may attenuate vigilance and contribute to cognitive complaints.

KEY WORDS

Temperature, Circadian, Alzheimer, MCI

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TITLE
MAPPING QUANTITATIVE TRAIT LOCI FOR FEBRILE SEIZURE

AUTHORS

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ABSTRACT

Febrile seizures (FS) are the most common seizure type in children affecting 2-5% of the population and occurring between the age of 6 months and five years. Recent association, family and twin studies indicate a genetic component in FS susceptibility. The aim of this study is to identify quantitative trait loci (QTL's) for FS susceptibility using a forward genetic strategy employing a panel of mouse chromosome substitution strains (CSS) based on the A/J (donor) and C57BL/6J (host) strain. Fever was induced by a hot-air stream of 50 °C for 900s at postnatal day 14. EEG recording confirmed that the start of tonic-clonic seizure co-incides with the onset of spike wave discharge in the hippocampus. Tonic-clonic seizure latency was determined in both genders of the host strain (C57BL/6J, n=40), the donor strain (A/J, n=9) and across the CSS panel (n=9/strain) as a phenotypic measure for FS susceptibility.

Five CSS carrying a QTL were identified. Behavioural phenotyping and genetic mapping of a F2-progeny (n=144) from one of these CSS resulted in a significant peak at this stage with a LOD-score > 6 (using MapQTL software). Thus, screening the CSS panel showed that FS susceptibility in mice is defined by multiple genetic loci, confirming that FS is a complex disorder. We identified a QTL involved in this FS susceptibility as a first step in the identification of the genes underlying this trait.

KEY WORDS

Febrile seizures, Quantitative trait loci, chromosome substitution strains

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TITLE**GFAP δ EXPRESSION IN NEUROGENIC ASTROCYTES IN THE DEVELOPING AND ADULT BRAIN****AUTHORS**

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ABSTRACT

Glial fibrillary acidic protein (GFAP) is an intermediate filament protein type III and considered to be a highly specific marker for astrocytes. In the last decade it has become clear that a subgroup of the GFAP-expressing cells located in the subventricular zone (SVZ) are the neural stem cells in the adult rodent and human brain. These cells proliferate to produce progenitors, which in turn generate neuroblasts which migrate through the rostral migratory stream (RMS) to form new interneurons in the olfactory bulb. Our group has identified an isoform of GFAP, termed GFAP δ , which is specifically expressed in SVZ astrocytes and therefore can be used to identify potential neurogenic astrocytes.

Our aim is to study the expression of GFAP δ in other brain areas involved in the neurogenic pathway in the adult brain and to provide evidence for the neurogenic capacity of these cells by performing double stainings with proliferation markers. Since during neural development, astrocytes and neurons are derived from radial glia, which are considered to be the neuronal precursors in the fetal brain, we questioned whether GFAP δ is expressed in these cells in the ventricular zone of the developing brain. To study this, we evaluated GFAP δ expression in human fetal brains ranging in age from 9 to 40 gestational weeks and in the brains of young infants.

We have demonstrated the expression of GFAP δ in several regions along the neurogenic pathway, such as the RMS and the olfactory bulb and we have shown co-localization of GFAP δ with proliferation markers. During development, GFAP δ expression was found in radial glia in the ventricular zone from 13 gestational weeks on. Later, expression shifted towards the SVZ, where expression remained until adulthood. GFAP δ -expressing radial glia and SVZ cells during brain development co-localize with stem cell markers nestin and vimentin and proliferation marker Ki67.

GFAP δ is thus a potential marker to distinguish neurogenic astrocytes from other astrocytes in the adult and the developing brain. Future studies including neurosphere assays should proof if GFAP δ is a specific marker for neural stem/progenitor cells.

KEY WORDS

Neural stem cells, astrocytes, GFAP, human brain development

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TITLE**ACCUMULATED DNA DAMAGE CAUSES AGE-RELATED COGNITIVE DECLINE****AUTHORS**

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ABSTRACT

Age-related cognitive decline and neurodegenerative diseases are a growing challenge for western societies. Accumulated DNA damage is thought to be a major factor underlying aging and could be a significant contributor to these impairments but direct proof of this hypothesis is lacking. Here we show that *Ercc1^{0/-}* mice, which are deficient in Nucleotide Excision Repair, show an age-dependent decrease in learning and neuronal plasticity, indicating that accumulated DNA damage is sufficient to induce cognitive decline upon aging.

KEY WORDS

Aging, plasticity, hippocampus, learning

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TITLE**SEX-DEPENDENT EFFECTS OF EARLY LIFE STRESS ON THE HIPPOCAMPUS****AUTHORS**

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ABSTRACT

Stress affects both structure and function of the hippocampus. Adult hippocampal neurogenesis is inhibited by stress and stress hormones. The impact of stress is generally more pronounced when applied early in life. In rat pups, maternal behaviour ensures a “stress-hypo-responsive” period between postnatal day (PND) 3 and 14. This period coincides with postnatal development of the hippocampal dentate gyrus (DG) and with maximal levels of neurogenesis. We hypothesized that maternal deprivation at the beginning of this period will influence neurogenesis and alter the structural make up of the adult hippocampus: this could potentially influence network properties later in life. To investigate this, we subjected rat pups to 24 hours of maternal deprivation at PND 3. Changed maternal care due to the experimental procedure were monitored during the first postnatal week. We studied several aspects of the hippocampal dentate gyrus at different timepoints: PND4, PND21 and in adulthood. To analyze neurogenesis survival, proliferation, neuronal differentiation and the number of astrocytes in the dentate gyrus were quantified. In addition, the degree of long term potentiation (LTP) and neuronal reconstruction was performed in adult rats.

We found no differences between groups in cell survival or proliferation rate at PND21. Analysis of neuronal maturation (doublecortin+ cells) revealed an increase in males, but a decrease in females due to maternal deprivation. We are presently studying the functional consequences for DG long-term potentiation and dendritic complexity of granular cells.

We conclude that maternal deprivation induces sex-dependent differences in DG neurogenesis, without affecting newborn cell survival or DG volume. This points to sex-dependent changes in maturation speed of young neurons, or a difference in cell-fate determination following exposure to early life stress.

KEY WORDS

Rat, maternal deprivation, early life stress, dentate gyrus, doublecortin, neurogenesis, GFAP, astrocytes, sex-differences

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TITLE
MADMAX COORDINATES EXOCYTOTIC RAB6 VESICLE TRANSPORT AND REGULATES NEURONAL DEVELOPMENT

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ABSTRACT

Active transport along microtubules plays a crucial role in neuronal development. Kinesin and dynein motors actively transport a large variety of cargoes in either a plus- or a minus-end directed motion along microtubules and are essential for neurite outgrowth. Most of the microtubule dependent motor proteins have been identified; however, the mechanisms that specify and regulate motor/cargo attachment are poorly understood. In this study we identify a novel adaptor protein, Madmax, which is able to attach exocytotic Rab6 vesicles to motor complexes and regulate neuronal development.

Madmax has strong homology to the Bicaudal D (BICD) family of proteins and is predominantly expressed in kidney and brain. Madmax co-precipitates dynein/dynactin and kinesin-3 and binds directly to the GTP-bound form of Rab6. Immunocytochemical analysis in Vero cells revealed that endogenous Madmax localizes to a subset of Rab6 positive secretory vesicles located around the centrosome. While knock-down of Madmax prevents the pericentrosomal localization of Rab6, overexpression of Madmax causes the accumulation of Rab6 vesicles, dynein/dynactin and kinesin-3 motor complexes at the centrosome. Live imaging of cells expressing GFP-Rab6 and Madmax showed an increase in the motility of Rab6 vesicles in both the microtubule minus- and plus-end direction.

In developing hippocampal neurons, Madmax is present in a vesicle-like pattern in both the cell body as well as in neurites and partially colocalizes with the exocytotic marker, GFP-NPY. Expression of a dominant negative form of Madmax in cultured neurons leads to a significant reduction in neurite outgrowth. We propose that the motor/cargo adaptor protein Madmax coordinates Rab6 vesicle transport by microtubule motors of opposite polarity and plays a role in neuronal development.

KEY WORDS:

Intracellular transport, neuronal development

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TITLE

ALTERNATIVELY AND CLASSICALLY ACTIVATED MACROPHAGES VARY IN MIGRATORY CAPACITY AND MIGRATE DIFFERENTLY IN ORGANOTYPIC CNS CULTURES

AUTHORS

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ABSTRACT

It is widely recognized that macrophages play an important role in the pathogenesis of multiple sclerosis (MS), having both beneficial and detrimental effects. Depletion of infiltrating macrophages has a suppressive effect on clinical signs of EAE. Conversely, elimination of macrophages leads to impaired remyelination after lyssolecithin induced demyelination. Different subtypes of macrophages exist with different functions in immune response and tissue repair. Two extremes are classically activated (CA) macrophages, which can be cytotoxic, and alternatively activated (AA) macrophages, which can be growth promoting. Indications that both types of macrophages are present in MS lesions have been found, with iNOS positive CA being located mostly at the active border and MR positive foamy macrophages with characteristics of AA macrophages more in the center of the lesion and perivascular. Due to these differences in localization our question became whether differently activated macrophages migrated differently and could be attracted by different cell types in the central nervous system (CNS).

We studied the migration of differently activated macrophages in organotypic CNS cultures and the effect of either demyelination or neuronal damage on migration. Finally, the intrinsic migratory capacity of macrophages was studied by directed migration over a filter under the influence of chemokines.

A higher number of AA macrophages migrated into untreated spheroids compared to CA macrophages. This difference in migration was also seen after the induction of demyelination or neuronal damage. Both CA and AA macrophages could migrate deep into the spheroids and reach neuronal cell bodies and axons, however this happened more frequently for AA macrophages.

To determine the intrinsic migratory capacity of different macrophages, migration across a filter in a blind well chamber was studied. A higher number of AA macrophages migrated in response to chemokines compared to CA macrophages. Furthermore, AA macrophages migrated significantly more towards neuronally conditioned medium, while CA macrophages migrated significantly more towards astrocyte- and oligodendrocyte- conditioned medium.

In summary, the intrinsic migratory capacity of AA macrophages appears to be greater compared to CA macrophages, under different conditions. AA macrophages are more attracted towards neuronally derived factors, implying that they might be involved in neuronal rescue during MS. CA macrophages are more attracted towards astrocytes and oligodendrocytes, implying a role in demyelination and inflammation.

KEY WORDS

Macrophages, MS, migration, classically and alternatively activated

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TITLE**P-GLYCOPROTEIN IS A NOVEL IMMUNOMODULATOR IN MULTIPLE SCLEROSIS****AUTHORS**

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS), characterized by the presence of sclerotic lesions throughout the brain. The mechanisms of CNS inflammation involve activation of autoreactive, myelin specific T helper (TH) cells in the periphery, which gain entry to the CNS and form perivascular infiltrates, a process that is accompanied by enhanced permeability of the blood-brain barrier (BBB). However, not all players of the inflammatory process are known yet. Our recent findings suggest that P-glycoprotein (P-gp) is a novel immunomodulator during MS. P-gp is an ATP-dependent membrane pump originally identified at the BBB where it actively removes unwanted compounds from the brain. P-gp is however also present on various leukocytes where it is postulated to mediate the release of cytokines and as such P-gp may influence maturation and emigration of antigen presenting cells. In humans, a single gene MDR-1 encodes P-gp, whereas in mice the gene is coded by both the *mdr1a/1b*. In *mdr1a/1b*^{-/-} animals, it has been shown that cytokine levels in the blood are somewhat lower. However, no data exist on the role of P-gp in the immune response. Therefore, the aim of current study was to elucidate the role of P-gp in immunological and inflammatory processes like MS and its animal model EAE. Here we describe that upon induction of EAE, *mdr1a/1b*^{-/-} animals have significantly reduced clinical symptoms and disease onset is delayed compared to wild-type animals. Furthermore, lymph node cells from *mdr1a/1b*^{-/-} mice showed strikingly decreased T cell proliferation and reduced secretion of inflammatory cytokines like INF- γ and TNF- α . Moreover, leukocytes from *mdr1a/1b*^{-/-} animals have reduced migration capacity across the mouse brain endothelial cells, and P-gp inhibition significantly blocks transmigration of human monocytes and CD4⁺ T cells across the BBB in vitro. Taken together, we here show a unique new physiologic function for P-gp, which may open new therapeutic avenues to interfere in the pathogenesis of several neuro-inflammatory diseases like MS.

KEY WORDS

P-glycoprotein, blood-brain barrier, Multiple Sclerosis, MDR, EAE

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TITLE**MIMICKING PROTEASOMAL RELEASE OF POLYGLUTAMINE PEPTIDES USING A NOVEL CELL-BASED TOOL****AUTHORS**

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ABSTRACT

Several neurodegenerative disorders, including Huntington's disease, are caused by expansion of the polyglutamine (polyQ) tract over 40 glutamines in the disease-related protein. Protein fragments containing the expanded polyQ tract are thought to initiate aggregation and represent the toxic species. While it is not clear how these toxic fragments are generated, *in vitro* data suggest that proteasomes release pure polyQ peptides upon degradation of proteins containing polyQ tracts. To examine whether the released polyQ peptides initiate aggregation in living cells, we designed a tool to express polyQ peptides of variable lengths to mimic polyQ peptide generation by the proteasome. Expression of a GFP-ubiquitin-polyQ construct led to subsequent release of polyQ peptides lacking the commonly used starting methionines or additional tags. We show that expanded polyQ peptides alone accumulate and are sufficient to initiate the aggregation process. As observed in polyQ disorders, essential components of the ubiquitin-proteasome pathway and chaperones were sequestered into these aggregates. Various proteins containing either wild-type or expanded polyQ stretches were also sequestered. Importantly, the generated expanded polyQ peptides were toxic to neuronal cells. This novel method mimics proteasomal release of polyQ peptides into living cells and enables the study and manipulation of the initial steps of protein aggregation and toxicity. Recent data suggest that these polyQ peptides can be cleared by the manipulation of several peptidases downstream of the proteasome.

KEY WORDS

Huntington's disease, polyglutamine (polyQ) , aggregation, proteasome, toxic fragments

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TITLE

AGGREGATION OF EXPANDED, PURE POLYGLUTAMINE PEPTIDES CAN BE INHIBITED BY OVEREXPRESSION OF THE CHAPERONES DnaJB6 AND DnaJB8

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ABSTRACT

Several neurodegenerative disorders, including Huntington's disease, are caused by expansion of the polyglutamine (polyQ) tract over 40 glutamines in the disease-related protein. Protein fragments containing the expanded polyQ tract are thought to initiate aggregation and represent the toxic species. While it is not clear how these toxic fragments are generated, in vitro data suggest that proteasomes release pure polyQ peptides upon degradation of proteins containing polyQ tracts. We designed a tool to express pure polyQ peptides of variable lengths in living cells to mimic polyQ peptide generation by the proteasome. Expression of a GFP-ubiquitin-polyQ construct led to subsequent release of pure polyQ peptides lacking the commonly used starting methionines or additional tags. In contrast to short polyQ peptides, polyQ peptides of disease-related lengths accumulated and were sufficient to initiate aggregation (Raspe et al., submitted). Since these aggregating polyQ peptides may represent a common mechanism in different polyQ disorders, we used this model to examine the role of proteases, chaperones and autophagy on polyQ peptide clearance. Here, we examined the effect of two members of the chaperone Hsp40-family, DnaJB6 and DnaJB8, which are able to suppress the aggregation of huntingtin-Q110 and reduce cytotoxicity. We show that these chaperones were also able to suppress the aggregation of expanded polyQ peptides drastically. This suggests that these chaperones act at the level of aggregation-initiating polyQ fragments. These chaperones may therefore be good candidates to repress aggregation of various polyQ disorders. Currently we are examining the effect of these chaperones on polyQ-induced cytotoxicity, as this would be an interesting point for therapy.

KEY WORDS

PolyQ aggregation, polyQ clearance, neurodegeneration, chaperones, autophagy

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TITLE

SYNTHESIS OF ¹⁸F-LABELLED CUBYL-WAY

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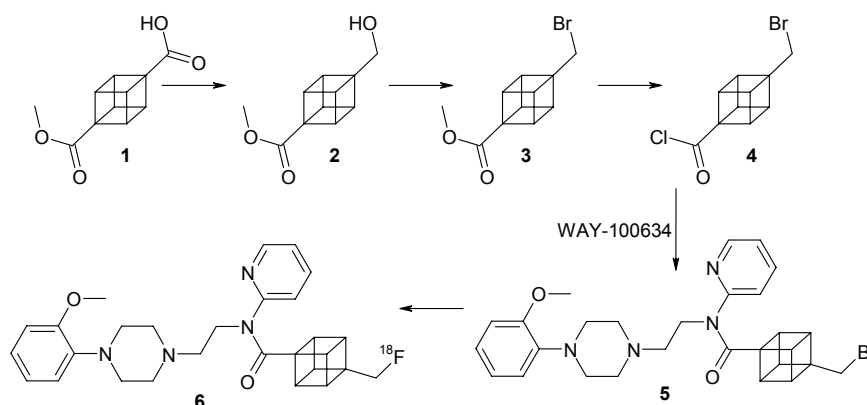
ABSTRACT

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 5-HT_{1A}-receptor. Furthermore we have shown that each of [¹²³I]iodocubyl-WAY and [¹⁸F]fluorocubyl-WAY bind to this receptor in rat brain and the hydrolysis rate of both which are incubated with human hepatocytes is much lower than MPPF. Moreover, [¹²³I]iodocubylDesmethylWAY is also synthesised and examined.

Results

Reduction of **1** with BH₃.SMe₂ in dry THF under argon gave **2** in 70% yield. Further bromination with CBr₄/triphenylphosphine in THF under argon gave **3** in 80% yield. The ester was then saponified with NaOH and subsequently treated with SOCl₂ 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 ¹⁸F in dry MeCN using kryptofix and K₂CO₃ 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.

Conclusion

A simple high- yield synthesis for a nca ¹⁸F- labelled analogue of WAY-100635 has been developed. Affinity and selectivity of this compound *in vitro* has been studied. The tracer is rapidly cleared from the blood and shows good brain uptake in the ROI. A comparison between the three radioligands ([¹²³I]iodocubyl-WAY, [¹⁸F]fluorocubyl-WAY and [¹²³I]iodocubylDesmethylWAY) was done. There is no significant difference in brain uptake between [¹²³I]iodocubylDesmethylWAY and [¹⁸F]fluorocubyl-WAY as well as between [¹²³I]iodocubylDesmethylWAY and [¹²³I]iodocubylDesmethylWAY in cortex, while [¹⁸F]fluorocubyl-WAY has showed the highest affinity in hippocampus.

KEY WORDS

WAY-100635, Cubane, 5-HT_{1A}, fluorination

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TITLE

DO PITX3 AND EN1 INTERACT IN THE MESODIENCEPHALIC DOPAMINERGIC (MDA) SYSTEM?

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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**ELECTROPHYSIOLOGICAL CHARACTERIZATION OF CONNEXIN 55.5. AND CONNEXIN 52.6****AUTHORS**Jorrit B. van Asselt, Y. Claassen, M. Kamermans**DEPARTMENT/INSTITUTE**

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ABSTRACT

Hemichannels are half gap-junctions, creating electrically conductive pores in the cell-membrane. A group of these hemichannel forming proteins are Connexins (Cx), of which Cx55.5 is located specifically and exclusively at the horizontal cell dendrites. At this location hemichannels could mediate the feedback from horizontal cells to photoreceptors by affecting the extracellular electric potential in the synaptic cleft between these cells. The importance of Cx55.5 is illustrated by the fact that feedback responses were greatly reduced in cones of zebrafish that express a non-functional Cx55.5 in the retina. In this study oocytes of *Xenopus Laevis* were used as a tool in order to acquire a full biophysical characterization of the zebrafish Cx55.5 and Cx52.9, in order to assess its possible role in the retina.

Oocytes were injected with RNA coding for Cx55.5 and used in two electrode voltage clamp (TEVC) experiments. Calcium dependent currents were observed in Cx55.5 injected oocytes but not in control injected, indicating the presence of Cx55.5 hemichannels. Pharmacological blocking agents were tested and Cx55.5 hemichannels were characterized for extracellular calcium dependence. In addition, the blocking effect of HEPES, a strong artificial buffer, on Cx55.5 was studied. Data concerning Cx 52.9 is being generated at the time of this writing.

Cx55.5 is able to form hemichannels in oocytes. These hemichannels show a decreased conductivity at depolarizing potentials in response to calcium, in a dose-dependent manner. In the physiological range of membrane potentials, calcium dependent conductance changes were observed. This indicates that Cx55.5 is likely to play an important role in the processing in the retina.

KEY WORDS

Connexin, electrophysiology, retina

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TITLE**INHIBITION IN THE CEREBELLAR CORTEX – THE ROLE OF INTERNEURONS IN MOTOR LEARNING.****AUTHORS**

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ABSTRACT

Studies on cerebellar motor learning and adaptation have long been focused on the role of plasticity phenomena (such as LTP and LTD) at excitatory synapses. Here, we tried to unravel the role of cerebellar molecular layer inhibitory interneurons, stellate and basket cells, in motor learning. In order to study their function, we performed several experiments on Purkinje cell specific mutant mice that lack GABAA-receptor gamma2 subunit required for GABAergic inhibition onto Purkinje cells. We investigated motor reflexes (OKR and (V)VOR), motor learning and cerebellar neurophysiology of these mutants in order to determine whether these alterations have an impact on cerebellar functioning. In addition, we performed extracellular in vivo recordings of Purkinje cells at rest, with optokinetic stimulation and during vestibular stimulation before and after motor learning. The results show a significantly higher regularity of simple spike firing in Purkinje cells of mutant compared to wildtype mice. The mutant mice also show significant difficulties in consolidation of motor adaptation, whereas their performance is only slightly affected. The results of this study indicate that stable temporal patterns of simple spike activities are required for proper consolidation of cerebellar motor learning.

KEY WORDS

Cerebellum, inhibitory interneurons, motor learning

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TITLE
NEUROGENIC ASTROCYTES IN THE ADULT HUMAN BRAIN HAVE A SPECIALIZED INTERMEDIATE FILAMENT NETWORK

AUTHORS

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ABSTRACT

The adult human brain contains two main regions where constitutive neurogenesis takes place, the subgranular zone and the subventricular zone (SVZ). In the SVZ, neural stem cells proliferate to produce fast-dividing neural progenitor cells, which migrate through the rostral migratory stream and differentiate to form new inter-neurons in the olfactory bulb. Studies in both rodent and human brain provide evidence that a subgroup of astrocytes, lining the ventricles, is the stem cell pool in the SVZ. In our group, we have identified a protein, GFAP- δ , which is highly expressed in a subpopulation of astrocytes in the SVZ, and is thus a potential marker for neural stem cells. Our aim is to study the population of GFAP- δ positive SVZ astrocytes to determine whether these astrocytes are indeed neurogenic, and to decipher the function of GFAP- δ in these cells.

In a first approach, we have investigated the expression of GFAP- δ throughout the SVZ, rostral migratory stream, and olfactory bulb as well as double-labeling with various markers for neurogenesis. In these experiments we have shown that GFAP- δ expressing cells can be found throughout the neurogenic system and co-express proliferation markers, such as PCNA and stem cell markers, such as nestin.

For our second, *in vitro*, approach, we have successfully established neurosphere cultures from post-mortem human adult brain material, obtained from the Netherlands Brain Bank. So far, we have shown the presence of GFAP- δ with qPCR and immunohistochemistry in these neurospheres. Also, we have evaluated GFAP- δ expression during differentiation of the neural precursors into astrocytes and neurons. Currently, we are further examining the function of GFAP- δ in neurogenic astrocytes. Not much is known about its function, but we have shown previously that GFAP- δ is assembly-compromised and can also change the properties of the GFAP filament network.

Our current results provide evidence that GFAP- δ is a marker for stem cells in the adult human brain, as it is expressed in proliferating, nestin-positive cells in the brain, as well as in an *in vitro* stem cell model, the neurospheres.

Acknowledgement

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Human brain material provided by the Netherlands Brain Bank

KEY WORDS

Adult neurogenesis, human, subventricular zone, neural stem cells, astrocytes, GFAP, neurosphere assay

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TITLE**DIFFERENTIAL ROLE FOR BASOLATERAL AMYGDALA AND PREFRONTAL CORTEX IN CRF-INDUCED ALTERATIONS IN STARTLE REACTIVITY****AUTHORS**

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ABSTRACT

Altered central corticotropin-releasing factor (CRF) signaling has been associated with psychotic features. To further study the role of central CRF signaling in psychotic features, we studied the effect of local CRF infusion on prepulse inhibition (PPI), a measure of information processing. PPI is disrupted in patients with psychotic features and following intracerebroventricular infusion of CRF in rodents. We specifically studied the role of the basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) herein. Canulas were placed bilaterally in either the BLA or mPFC of Wistar rats. After recovery, animals were infused with CRF or vehicle for 5 days and acute (day 1), subchronic (day 5) and post-treatment (7 days after treatment ended) effects on PPI were measured. CRF treatment into the BLA, but not the mPFC, decreased both habituation (acutely and subchronically) and PPI (subchronically). 7 days post-treatment CRF-induced effects on PPI and habituation were normalized. Altogether, data show that the BLA might be important in the PPI-disrupting effects of CRF.

KEYWORDS

Corticotropin-releasing factor, startle, prepulse inhibition, basolateral amygdala, prefrontal cortex

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TITLE**HIGH-CONTENT SCREENING OF GENE CANDIDATES FOR PARKINSON'S DISEASE****AUTHORS**

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopamine neurons in the substantia nigra. Pathogenic mutations and environmental factors are thought to cause PD due to a complex interaction of multiple factors, including mitochondrial dysfunction, oxidative damage, and abnormal protein aggregation and phosphorylation. Although several gene mutations are known to either cause PD or increase PD incidence (e.g., SNCA, DJ1, PINK1, Parkin, UCH-L1 and LRRK2), there is no clear understanding of PD etiology and no effective treatment exists yet. Previous microarray studies on human post mortem substantia nigra tissue identified 287 genes that are differentially expressed in PD patients compared with healthy control subjects (Bossers et al., 2008). Our aim is to functionally characterize these genes in an in vitro cellular model for PD. We use human SH-SY5Y neuroblastoma cells, and developed a high-content screening assay that addresses various aspects of neurodegeneration, including cell viability, mitochondrial function, cytoskeletal integrity, neurite outgrowth and apoptosis, in a high-throughput manner. siRNA-mediated knock-down will be used to systematically analyze the role of PD gene targets. Gene function will be assessed in healthy cells and in cells with increased vulnerability towards degeneration due to the exposure to a sublethal concentration of MPP⁺ or the combined knock-down of known PD associated genes. These experiments will provide novel insights into common molecular pathways involved in PD and may identify novel drugable targets that can be used in treatment therapies.

Reference

Bossers *et al.*, 2008, Brain Pathology, in press.

KEY-WORDS

Parkinson's disease, neurodegeneration, SH-SY5Y, MPP⁺, siRNA, high-content screen

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TITLE**PSYCHOSIS AND AUTISM. AN IN VIVO MAGNETIC RESONANCE IMAGING STUDY OF BRAIN ANATOMY****AUTHORS**

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ABSTRACT

Introduction: Autistic Spectrum disorder (ASD) is increasingly recognised, with recent studies estimating that 1% of children in South London are affected. However the biology of co-morbid mental health problems in people with ASD is poorly understood. The aim of this study was to investigate the brain anatomy of ASD people with and without psychosis.

Method: We used in vivo magnetic resonance imaging and compared 16 adults with ASD to 14 adults with ASD and a history of psychosis. Both groups were also compared to a group of 16 healthy controls.

Results: Compared to controls both ASD groups had significantly less grey matter bilaterally in the temporal lobes (including the fusiform gyrus) and cerebellum, and reduced white matter in the cerebellum. In contrast they had increased grey matter in striatal regions. However those with psychosis also had a significant reduction in grey matter content of frontal and occipital regions. Contrary to our expectation, *within* ASD, comparisons revealed that psychosis was associated with a bilateral reduction in grey matter of cerebellum and the fusiform gyrus.

Conclusions: The biology of psychosis in people with ASD is different from that in the non-autistic population. The presence of neurodevelopmental abnormalities normally associated with ASD may modify the threshold (i.e. 'tipping-point') into psychosis.

KEY WORDS

Autism psychosis VBM anatomy

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TITLE**FLEXIBILITY OF BEHAVIOURAL PLANNING IN MOUSE PREFRONTAL CORTEX****AUTHORS**Marieke de Boer, M.M.G. Koenis, M. van der Roest, A.B. Mulder**DEPARTMENT/INSTITUTE**

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ABSTRACT

The prefrontal cortex (PFC) is mainly involved in aspects of behavioural planning. This is reflected in the flexible way in which an animal adapts behaviour according to altered rules. Not much is known about the neuronal mechanisms underlying the involvement of the medial PFC (mPFC) in flexibility. Therefore, we aim to study these mechanisms in the mPFC of freely behaving adult male C57BL/6 mice, by recording the mPFC unit activity and local EEG with use of a multiple tetrode drive (Neuralynx, 16 channels) linked to a Plexon data acquisition system. We designed a task apparatus consisting of a stimulus light on one side and a reward area with a food tray on the other side, separated by a 0.5m long passage. In summary, mice are required to make a nose poke as a response to the stimulus light, triggering the illumination of the reward light, which means that the mouse can collect its reward. When the mouse runs back towards the stimulus light, the crossing of an infrared detector starts a new trial. All mice mastered this task within a total of 30 training-sessions. After tetrode implantation, the first trials are the same as before, however, halfway the session there is a 50% chance that the reward light will switch off when the mouse is on route to collect its reward. This will cause uncertainty about the rule the mouse learned. The mPFC activity might shed light on the neuronal mechanisms underlying this uncertainty and the flexibility to change planning and behaviour.

KEY WORDS

mPFC, flexibility, mouse

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TITLE**SOCIAL DEFEAT STRESS AND SUBSEQUENT ANTIDEPRESSANT OR BEHAVIORAL THERAPY****AUTHORS**Pieter van Bokhoven¹, J.E. van der Harst³, W.J.G. Hoogendijk², A.B.Smit¹, S. Spijker¹.**DEPARTMENT/INSTITUTE**¹Dept. of Molecular & Cellular Neurobiology and ²Dept. of Psychiatry, Center for Neurogenomics & Cognitive Research, VU University and VU Medical Center, Amsterdam, and ³Deltaphenomics B.V., Wageningen.**ABSTRACT**

Chronic stress induced by social defeats (SD) in rat inter-male confrontations followed by subsequent long-term individual housing has been shown to produce a unique behavioral phenotype directly relevant to depression. This includes reduced sensitivity to reward (anhedonia) and impaired cognitive behavior. The insensitivity to rewards were shown to be restored by chronic administration of an antidepressant drug or by behavioral therapy consisting of regular transfer to an enriched cage. However, the molecular mechanisms underlying the onset of these symptoms as well as their reversal by antidepressant or behavioral therapy remain largely unknown. As preliminary data showed changes in synapse physiology in SD animals, we aim to identify differentially expressed proteins in striatal and hippocampal synaptic membranes after SD stress and after subsequent antidepressant or behavioral therapy. Additionally, neurogenesis in the dentate gyrus of the hippocampus will be analyzed, since in several animal models of depression cell proliferation was reduced in this region. By correlating synaptic protein expression with observed depressive symptoms, as well as with data on cell proliferation, we aim to identify neuroplastic changes that lie at the basis of depressive phenotypes, and thereby reveal new potential molecular targets of drugs that can alleviate these symptoms. Here we provide ample experimental setup and present the first data on this series of experiments focusing on physiological parameters of animals engaged in the social defeat paradigm.

KEY WORDS

Social defeat, antidepressants, synapse physiology

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TITLE**IDENTIFYING MOLECULAR MECHANISMS UNDERLYING SECRETORY VESICLE RELEASE IN NEURONS****AUTHORS**Rhea van de Bospoort, S.K. Schmitz, M. Verhage, R.F.G. Toonen**DEPARTMENT/INSTITUTE**

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ABSTRACT

Neuromodulatory peptides and hormones are packaged into dense core vesicles (DCVs) that play critical roles in many biological processes, ranging from neuronal survival to memory formation. In contrast to synaptic vesicles, DCV release is not restricted to the nerve terminal and relatively little is known about the proteins that participate in DCV release. Here we have made use of a genetically-encoded reporter of dense-core vesicle secretion, Semaphorin 3A coupled to pH-sensitive EGFP (Semaphluorin), to study dense-core vesicle release in mouse hippocampal neurons using live cell imaging. To elucidate the molecular pathway and to identify potential differences with synaptic vesicle release, we focused on the role of a set of proteins (SNARE proteins, Munc13 and Munc18) that are essential for synaptic vesicle secretion. Here we show that in contrast to synaptic vesicles, the SNARE protein synaptobrevin and Munc13 and Munc18 are not essential for DCV release. These results suggest a different requirement for synaptic proteins in DCV secretion compared to synaptic vesicle release.

KEY WORDS

LDCV, exocytosis

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TITLE

DELTA9-TETRAHYDROCANNABINOL INDUCES DOPAMINE RELEASE IN THE HUMAN STRIATUM

AUTHORS

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ABSTRACT

Introduction: Addictive drugs are thought to induce their rewarding effects by enhancing synaptic dopamine levels in the striatum [1]. Using positron emission tomography (PET), increased striatal dopamine levels have been demonstrated after administration of amphetamine, cocaine, alcohol and nicotine. In animal models, it has been shown that cannabinoid substances such as $\Delta 9$ -tetrahydrocannabinol (THC), the main psychoactive component in cannabis, also stimulate striatal dopamine neurotransmission [2]. At present, however, it is not known whether THC affects the human striatal dopamine system. Therefore, the purpose of the present study was to investigate whether THC can induce dopamine release in the striatum of healthy human subjects.

Methods: A double-blind, randomized, placebo-controlled, cross-over study was performed. Seven healthy male subjects underwent two PET scans after administration of either 8 mg THC or placebo using a Volcano® vaporizer (Storz-Bickel GmbH, Tuttlingen, Germany). Scanning sessions were separated by at least two weeks and all subjects had a history of mild cannabis use for at least one year. Dopamine release in striatal subregions was assessed by determining changes in binding potential (BP_{ND}) of the dopamine D₂/D₃ receptor ligand [¹¹C]raclopride [3]. [¹¹C]raclopride was administered with a bolus and continue infusion. The bolus to infusion ratio (Kbol) was 112 minutes. BP_{ND} was calculated as DVR-1 with the cerebellum as a reference tissue. In addition, behavioral and subjective effects of THC were assessed using the Brief Psychiatric Rating Scale (BPRS) and two sets of Visual Analogue Scales. Venous blood samples were withdrawn to determine THC plasma concentrations.

Results: [¹¹C]raclopride BP_{ND} was significantly reduced in ventral striatum and precommissural dorsal putamen, but not in other striatal subregions, after inhalation of THC compared with placebo (see table). This is consistent with increased dopamine release in these striatal subregions after THC administration. In addition, THC induced well-known significant behavioral, subjective and physiological effects. Plasma concentrations of THC showed a maximum of 143 ± 91 ng/ml five minutes after inhalation, decreasing rapidly thereafter.

Conclusion: $\Delta 9$ -THC, the main psychoactive component of cannabis, induces dopamine release in the human striatum. This finding implies that THC shares a putatively addictive property with other drugs of abuse.

| Region | BP _{ND} Placebo | BP _{ND} THC | Difference (%) | p-values |
|-------------------------------|--------------------------|----------------------|----------------|----------|
| Ventral striatum | 1.40 ± 0.24 | 1.35 ± 0.24 | -3.43 ± 3.70 | 0.029 * |
| Precommissural dorsal caudate | 2.18 ± 0.25 | 2.12 ± 0.13 | -2.09 ± 6.44 | 0.355 |
| Precommissural dorsal putamen | 2.75 ± 0.24 | 2.64 ± 0.16 | -3.88 ± 4.07 | 0.042 * |
| Postcommissural caudate | 1.62 ± 0.19 | 1.55 ± 0.15 | -4.12 ± 7.14 | 0.157 |
| Postcommissural putamen | 2.74 ± 0.29 | 2.69 ± 0.20 | -1.50 ± 4.42 | 0.329 |
| Striatum | 2.28 ± 0.22 | 2.21 ± 0.12 | -2.57 ± 4.42 | 0.153 |

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KEY WORDS

THC, cannabis, dopamine, reward, addiction

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TITLE
GENOTYPES AND PHENOTYPES IN ANOREXIA NERVOSA

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ABSTRACT

Anorexia nervosa (AN) is a psychiatric disease with a well-documented heritability. The mechanisms of genetic susceptibility to AN remain largely unknown. In this study we begin with determining associations of candidate genes to the disease by comparing genotypes' distributions between cases and controls. Consecutively, in the AN group, we investigate the relations of associated genes to treatment course and outcome, personality traits assessed via psychological questionnaires and cognitive flexibility assessed by means of a neurocognitive task. The current poster presents an example of a genetic association between dopamine receptor D2 (DRD2) gene and AN (preliminary findings) and indicates possible following research steps, i.e. how the relation with quantitative (sub)phenotypes, such as personality traits or treatment outcome may be investigated.

KEYWORDS

Anorexia nervosa, eating disorders, gene association, endophenotypes, set-shifting, reward sensitivity, DRD2, Wisconsin Card Sorting Test

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TITLE
**SPECIFICITY OF RISK FACTOR FOR PSYCHOTIC SYMPTOMS IN THE GENERAL POPULATION;
ETHNICITY THE ODD ONE OUT?**

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ABSTRACT

Background

Studies have shown that schizophrenia and non-clinical psychotic symptoms in the general population share the same risk factors, suggesting the presence of a psychosis continuum. To our knowledge there are no large scale studies looking at the specificity of these risk factors for non-clinical psychotic symptoms in relation to other psychiatric symptoms in the general population.

Methods

In a general population sample of 4,894 subjects (mean age 39.0, 44.9 % men) from the Utrecht Health Project we investigated the relation between socio-demographical characteristic and non-clinical psychotic symptoms and other psychiatric symptoms measured with the SCL-90. We used two models; we examined the effects of risk factors on 4 groups of psychiatric symptoms with and without controlling for the presence from symptoms of another groups.

Results

Participants with psychotic symptoms had an 89% chance of having also depressive, anxiety or phobic anxiety symptoms. The risk profiles for psychotic symptoms and other psychiatric symptoms were similar. Only non-Dutch ethnicity was specifically associated with non-clinical psychotic symptoms.

Conclusion

Risk factors for psychotic symptoms also predispose for other psychiatric symptoms. In our study only non-Dutch ethnicity was specifically associated with non-clinical psychotic symptoms.

KEY WORDS

Schizophrenia, general population, psychotic symptoms, risk factors, SCL-90

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TITLE
VESICLE RELEASE SUPPORTS BUT IS NOT ESSENTIAL FOR DIRECTED OUTGROWTH

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ABSTRACT
In early development, neurons form neurites, each bearing a growth cone. Recent evidence suggests the presence of a vesicle fusion and release machinery at the tip of the growth cone, which is thought to depend in part on SNARE proteins. We studied the role of vesicle release on neurite outgrowth and morphology. We used both dissociated cell cultures and organotypic slice cultures of release deficient mice (munc18-1 null and munc13-1/2 double null). We found decreased neurite length and outgrowth speed in release deficient neurons. Morphology was altered in Munc18 1 null, but not WT or M13-1/2 double null neurons, with more and filopodia. The decreased outgrowth diminished on the long time scale of 2-4 weeks.

KEY WORDS
Vesicle release, outgrowth, brain development

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TITLE

A PUTATIVE RADIOLABELED LIGAND FOR IN VIVO IMAGING OF THE M1 MUSCARINIC ACETYLCHOLINE RECEPTOR BY PET

AUTHORS

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ABSTRACT

Background

The M1 muscarinic acetylcholine receptor (m1ACh-Rr) is the subtype with the highest density in the brain and belongs to the class of G-protein coupled receptors (GPCR); they are highly expressed in the basal ganglia, hippocampus, olfactory bulb and cortical areas. (1) Positron Emission Tomography (PET) has been applied to 'visualize' receptors in vivo, however, the usually applied antagonist PET ligands label the total pool of GPCRs and do not distinguish between the functionally-coupled and non-coupled receptors. An agonist PET ligand would only label functionally-coupled receptors and would provide a non-invasive tool to study the active m1ACh-receptors in vivo.

Objectives

Radiosynthesis of a m1ACh-receptor agonist and evaluation of its biodistribution and m1ACh-receptor selectivity in rats by ex vivo biodistribution experiments.

Methods

A ¹¹C-labeled m1ACh-R agonist was obtained via methylation of the precursor through addition of [¹¹C]CH₃I. The product was purified by HPLC and recovered from the HPLC eluent by solid-phase extraction. The ex vivo measured biodistribution was determined in male wistar rats, specificity of uptake of the tracer was assessed by pre-treatment with various blockers or saline as control. To measure total tracer uptake, rats received a iv bolus injection of 40 MBq radioligand, and were sacrificed at 5, 15, 30 and 60 minutes. Several organs and brain regions were dissected, weighed and counted for radioactivity. The pre-treated group was injected with a blocker (s.c.) 30 minutes prior to the iv bolus injection of the radioligand. Thirty minutes after the tracer injection the animals were sacrificed and handled as described above.

Results

The incorporated yield of [¹¹C]CH₃I was good and the ¹¹C-labeled m1ACh-R agonist was obtained with a high radio-chemical purity. Initial ex vivo biodistribution experiments showed a high brain uptake in the olfactory bulb, prefrontal cortex, cerebral cortex, basal ganglia and hippocampus. Various blockers were able to decrease the uptake of the radioligand in the m1ACh-R-rich brain regions.

Conclusion

A m1ACh-R agonist was radiolabeled successfully with ¹¹C. Regions in the rat brain, known to be rich in m1ACh-receptors, showed higher uptake. The tracer is further investigated in *in vitro* and *in vivo* imaging studies in animals

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KEY WORDS

M1 muscarine acetylcholine receptor; Agonist; Brain; Biodistribution; Autoradiography; ¹¹C; positron emission tomography.

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TITLE**RECURRENT CNVS DISRUPT THREE CANDIDATE GENES IN SCHIZOPHRENIA PATIENTS****AUTHORS**

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ABSTRACT

Schizophrenia is a severe psychiatric disease with complex etiology, affecting approximately one percent of the general population. Most genetic studies so far focused on disease association with common genetic variation such as single nucleotide polymorphisms, but recently it has become apparent that large-scale genomic copy number variants (CNVs) are involved in disease development as well. To assess the role of rare CNVs in schizophrenia, we screened 54 patients with deficit schizophrenia using Affymetrix' GeneChip 250K SNP arrays. We identified in total 90 CNVs, 77 of which have been reported previously in unaffected control cohorts. Among the genes disrupted by the remaining rare CNVs are MYT1L, CTNND2, NRXN1 and ASTN2, genes that play an important role in neuronal functioning but – except for NRXN1 – have not been associated with schizophrenia before. We studied the occurrence of CNV at these 4 loci in an additional cohort of 752 patients and 706 normal controls from The Netherlands. We identified 8 additional CNVs of which the 4, affecting coding sequences, were only found in the patient cohort. Our study supports a role for rare copy number variants in schizophrenia susceptibility and identifies at least three novel candidate genes for this complex disorder.

KEY WORDS

Copy number variation, schizophrenia, MYT1L, CTNND2, NRXN1, ASTN2, duplication, deletion, disruption

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TITLE
HIPPOCAMPAL CODING OF ROUTES AND SEQUENCES ON THE STARMAZE IN WILD-TYPE AND CA1 NR-1 KO MICE

AUTHORS

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ABSTRACT

The hippocampus is the central structure of the spatial navigation system. Hippocampal neurons are known to flexibly encode animal location, by synthesizing multiple streams of sensory and self-motion information. Moreover, hippocampal cells can encode temporal sequences of events and/or locations, with a variety of mechanisms, ranging from theta-phase coding during active behavior to forward and reverse sequence replay during inactivity. In addition, behavioral studies indicate that NMDA receptors in the hippocampal CA1 subfield are implicated in encoding of non-spatial relational memories. Previously (2006) Rondi-Reig et al. showed that transgenic mice with a CA1 knockout of the NMDA NR1 receptor subunit (NR1-KO) are impaired in a navigational task in which they have to find a submerged platform in a star-shaped maze. Such a task could be solved by using either an allocentric (distal-cue based) or a sequential egocentric (based on sequences of body turns) strategy. The patterns of behavioral results suggested that at least part of this deficit could be due to a (presumably hippocampal) impairment of behavioral-sequence encoding in the mutants. To elucidate the exact neural mechanisms supporting route-based memory in the hippocampus, it is necessary to study the hippocampal activity patterns occurring during navigation in the Starmaze. To this purpose, we developed a version of this task compatible with electrophysiology, and we are in the process of collecting samples of CA1 neural ensemble activity in mutants (NR1-KO) and control mice, during performance on the Starmaze, making use of a novel, ultra-light recording device allowing chronic placement of 6 tetrodes in the mouse brain. Our results so far suggest that KO mice also manage to learn our version of the task and make use of both allocentric and seq. egocentric strategies. Preliminary results indicate striking differences in the pattern of CA1 pyramidal neurons activity, as compared to what is known from rat studies, especially in the location-specific firing of these neurons, which seem to be much more disperse in our recordings.

KEY WORDS

Spatial navigation, electrophysiology, tetrode recordings, CA1-NMDAR KO mice

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TITLE
THALAMIC NETWORK RESPONSE TO OSCILLATORY ACTIVITY ASSOCIATED WITH PARKINSON'S DISEASE AND DEEP BRAIN STIMULATION

AUTHORS

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder which results in enhanced synchronized oscillatory activity in theta and beta bands (3-30 Hz) in the Basal Ganglia (BG) nuclei. Synchronized oscillatory activity observed in the BG nuclei is believed to interfere with the normal functioning of the motor system and lead to Parkinson's disease motor symptoms. In the advanced stages of the disease, Parkinson's disease motor symptoms are managed by surgical methods such as Deep Brain Stimulation (DBS) (Benabid 2003).

DBS is a reversible surgical treatment method which involves delivery of high frequency electrical pulses (120-180 Hz stimulation frequency, 0-5 V pulse amplitude, and 0.06-0.2 ms pulse duration) to specific BG nuclei, such as subthalamic nucleus (STN) or globus pallidus internum (GPI). Despite high clinical efficacy of DBS, the mechanism through which Parkinson's disease motor symptoms are suppressed, remains unknown (Benabid 2003).

While synchronous oscillatory activity in theta and beta ranges is widely associated with pathophysiology of Parkinson's disease, high frequency activity induced in the BG network during DBS is correlated with the suppression of Parkinson's disease motor symptoms. It still remains unknown what makes certain frequencies induced in the BG network "bad" and what makes the others "good"?

In order to address this question, we have extended our previous study on the frequency selective response of thalamocortical cells and we have implemented a bio-physical thalamic network model which included thalamic relay and reticular neurons (Mayer et al. 2006, Destexhe et al. 1998). Thalamus plays a fundamental role in the motor system by closing the cortico-BG loop. Thalamus receives glutamergic projections from the pre-motor cortex and gabaergic projections from the BG output nucleus and projects back to pre-motor cortex. P Brown et al. (2003) have proposed that low frequency oscillations observed in BG nuclei are transferred to cortex by thalamus; resulting in anti-kinetic oscillations in the pre-motor cortex. Effects of low frequency oscillatory BG activity and high frequency DBS induced activity on thalamic processing of cortical inputs could clarify why some frequencies induced in the BG network are associated with pathophysiology while others are associated with treatment. Our model has also been used in order to investigate if the thalamic network processes different cortical firing patterns and frequencies in a different way when the BG input is in the low frequency oscillatory state.

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TITLE**DELETION OF SCAP IN ASTROCYTES: THE IMPLICATION OF DISRUPTED LIPID METABOLISM IN THE MOUSE BRAIN****AUTHORS**

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ABSTRACT

Studies on neuron-glia interactions have revealed a wide spectrum of functions for astrocytes in the brain. Astrocytes support neurons and recently it was found that they also function as active partners in synaptic function in a so-called "tripartite synapse". Astrocytic function in neuronal differentiation and synaptic transmission involves soluble secreted factors and direct contact between astrocytes and neurons. In cell cultures it has been shown that astrocytes synthesize and secrete fatty acids and cholesterol, which were demonstrated to induce neurite outgrowth, synapse formation and maturation. Intracellular synthesis of these lipids involves SREBPs-cleavage activating protein (SCAP), which is required for activation of sterol response element binding proteins (SREBPs) that in turn activate the transcription of genes underlying lipid synthesis.

The brain is remarkably different in its lipid composition from other organs. It is highly enriched in poly-unsaturated fatty acids (PUFA) and cholesterol, which are, together with lipids, mostly synthesized locally. We hypothesize that astrocytes supply lipids to neurons during development and in the adult brain through the activation of SREBPs by SCAP. To test this, we used cre-lox based transgenesis to generate mice in which SCAP was deleted in cells expressing GFAP-cre (mainly astrocytes) starting at E14,5.

No phenotypical differences were observed in SCAP knockout animals at birth; however, we observed inducible startle-like behavior (hyperplexia/dystonia) with an onset at 2 months. Importantly, the number of startles increased during aging and correlated with a decrease in survival of the mice. Preliminary behavioral analysis shows that SCAP mutant mice have reduced anxiety-related behavior, increased exploration, and disturbance in motor behavior. SCAP mutant mice have smaller brains, whereas no difference was found in body weight. Hypotrophy of the cerebellum is one of the most evident anatomical changes.

KEY WORDS

Glia, SCAP, transgenesis, survival, brain hypotrophy

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TITLE**A COMPARISON OF NEURONS WITHIN THE MEDIAL-, AND LATERAL ENTORHINAL CORTEX****AUTHORS**Cathrin B. Canto^{1,2}; E.I. Moser¹, M-B. Moser¹, M.P.Witter^{1,2}**DEPARTMENT/INSTITUTE**¹ Centre for the Biology of Memory, NTNU, Trondheim, Norway, ² Dept. of Anatomy and Neurosciences, VU University medical center, Amsterdam**ABSTRACT**

The medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC) comprise a number of layers, each harboring a variety of neurons that are the elements of functional intrinsic and extrinsic networks. These regions play a role in processing of information that contributes to learning and memory. Neurons in the MEC of rats code information about position, directionality and velocity of a rat and may thus enable complex navigational behavior (Fyhn et al., 2004, Sargolini et al., 2006). The organization of the neuronal network in MEC which underlies the navigational functionality is unknown. Compared to the MEC the function of the LEC in the rat is not unraveled but we know that the LEC receives input from the perirhinal cortex, which in turn receives information from sensory modalities and most from olfactory domains. There is a difference in the function of the MEC and LEC in vivo, which might be due to differences in either the electrophysiological properties of individual neurons within the MEC and LEC, the morphology of neurons and thereby the connectivity of neurons, or both. The aim of our studies is to compare neurons in MEC and LEC anatomically and electrophysiologically. We found that MEC and LEC layer II neurons differ in electrophysiological and morphological properties. Cells in other layers are more similar in LEC compared to MEC.

KEY WORDS

Entorhinal cortex, morphology, electrophysiology, learning and memory

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TITLE

LIFETIME AT THE MEMBRANE: THE MOLECULAR FACTORS THAT INFLUENCE TETHERING AND DOCKING OF SECRETORY VESICLES AT THEIR TARGET

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ABSTRACT

Secretory vesicles in the nervous system and endocrine tissue contain a large variety of signaling molecules for cell-cell and humoral communication. These signaling molecules are released upon fusion of the vesicle with the target membrane. This fusion process is a tightly regulated process and many genes have been implicated in its regulation. A number of upstream events have to take place before a vesicle is fusion-competent. The first event is that vesicles become stably docked at the target by unknown molecular mechanisms. Several years ago, our lab was the first to identify a molecular factor essential for this first docking step, the *munc18-1* gene (see Voets et al 2001). Since this discovery, we have designed an assay to monitor tethering and docking of individual vesicles in living secretory cells, based on total internal reflection fluorescence (TIRF) imaging. Using this assay we aim to analyse the consequences of genetic and pharmacological manipulations of genes that may be involved in the tethering and docking of secretory vesicles.

KEY WORDS

Secretion, chromaffin cells, Total Internal Reflection Fluorescence (TIRF) microscopy, vesicle fusion

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TITLE**IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION OF NOVEL REPRESSORS OF NEURONAL REGENERATION****AUTHORS**

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ABSTRACT

Neuronal processes in the central nervous system (CNS) do not spontaneously regenerate after damage, which is the main reason for the irreversible and devastating effects of for instance spinal cord injuries. Damaged axons in the peripheral nervous system (PNS) on the other hand do spontaneously regenerate. Understanding the intrinsic differences in regenerative capacity between central and peripheral neurons will help to develop intervention strategies to promote neuronal regeneration in the CNS.

Dorsal root ganglion (DRG) neurons are an attractive model to study neuron-intrinsic mechanisms of regeneration. DRG neurons extend one axon into the spinal nerve and one axon into the dorsal root. The peripheral and central branches differ in their capacity to regenerate: a peripheral nerve lesion results in vigorous regeneration of injured axons, but after a dorsal root lesion regeneration of injured nerve fibres is significantly impaired. A microarray study was conducted to identify genes that are differentially expressed following peripheral and central DRG nerve crush (Stam et al., 2007). In a subsequent study, many of these genes were tested for their potential to regulate neurite outgrowth of DRG-like F11 cells. An intriguing finding in this study was that during successful DRG neuron regeneration (i.e., after peripheral nerve crush) several genes are upregulated that seem to suppress neurite outgrowth. These suppressors may in fact be part of conserved cellular networks, acting together with and fine tuning the effects of other regulators of neuronal outgrowth, as was shown for the transcription factors NFIL3 and CREB (MacGillavry et al., 2008). These findings suggest that one way to improve regeneration of damaged neurons is to inhibit expression of neurite outgrowth suppressors.

In this study, we try to functionally characterize the role of novel neurite outgrowth suppressors in F11 cells, in primary adult DRG neurons in culture, and in vivo. First, we will study the effects of knock-down and overexpression on neurite outgrowth. Next, we will use tagged overexpression constructs to study cellular localization. Finally, we will use co-immunoprecipitation to identify binding partners that may help to explain the cellular/molecular mechanisms of outgrowth suppression.

The identification, validation and understanding of negative regulators of neuronal regeneration provides a novel direction towards the development of therapeutic interventions strategies. Such an intervention would simply require reducing the activity of a protein, which in principle would be simpler and saver than overexpressing growth promoting genes.

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KEY WORDS

Neuronal regeneration, neurite outgrowth

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TITLE**SYNAPTIC PROTEOMICS OF RAT PREFRONTAL CORTEX AFFECTED BY ADOLESCENT NICOTINE EXPOSURE****AUTHORS**

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ABSTRACT

Adolescence is a developmental period, during which the brain and particularly the medial prefrontal cortical (mPFC) regions thereof have not yet fully matured. Because epidemiological data have suggested that adolescent nicotine use may result in disturbances in cognitive function in adulthood, we investigated the long-term molecular and behavioral effects of adolescent nicotine exposure in rats.

Male Wistar rats were exposed to 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. Visuospatial attention and impulsive action were tested in the 5-choice serial reaction time task, whereas impulsive choice was assessed in the delayed reward task. Another group of animals was pretreated as described above and decapitated at different time points before and after the pretreatment and compared with untreated adolescent animals in order to study developmental and nicotine-induced changes in the synaptic proteome of the mPFC.

Our data show that adolescent, but not post-adolescent, nicotine exposure affects cognitive performance in adulthood and results in diminished attentional performance and increments in impulsive action, while leaving impulsive choice intact. This altered cognitive performance appeared to be associated with enhanced releasability of dopamine in the mPFC. Using quantitative iTRAQ-based proteomics, we were able to detect small, but significant changes in synaptic proteins in the mPFC. Specifically during adolescent development of the mPFC many synaptic proteins show differences in expression, mostly between early adolescence (PND34) and adulthood (PND 79). In addition, nicotine exposure during adolescence differentially affects the developmental expression of some of these proteins.

Together, these data suggest that adolescence is a time window during which the brain is vulnerable to long-lasting synaptic and cognitive disturbances resulting from nicotine exposure.

KEY WORDS

Adolescence, nicotine, cognition, attention, impulsivity, proteomics

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TITLE
INNOVATIVE APPROACHES FOR COCAINE PHARMACOTHERAPY: THE CASE OF RIMONABANT

AUTHORS

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ABSTRACT

Rationale

In today's society, cocaine abuse and relapse remains a growing problem. Abstinent cocaine abusers have difficulties staying "clean", and good treatment strategies for preventing relapse to cocaine abuse are lacking. Dopamine receptor availability in the striatum is linked closely to dependence and relapse disorders, and neuro-imaging techniques allow us to investigate these effects.

Objectives

In a double-blind placebo-controlled clinical trial, our main goal is to investigate changes in dopamine D₂ receptor availability in abstinent cocaine users after administration of rimonabant (SR141716A), a selective cannabinoid 1 (CB₁) receptor antagonist.

Methods

For our study, thirty male detoxified cocaine abusers are divided into two groups: one group (n=15) who receive rimonabant, and another group (n=15) who receive placebo. Using SPECT, we assess changes in striatal D₂ receptor availability following acute and long-term rimonabant use compared to placebo-using detoxified cocaine abusers. Brain activation patterns due to cues previously associated with drug intake are studied in a cue-reactivity paradigm and assessed by functional magnetic resonance imaging (fMRI). Additionally, different tasks and questionnaires assess impulsivity, motivational value of drug-relevant stimuli, conflict monitoring, attentional bias, and subjective craving. Urine benzoyllecgonine tests are conducted in order to assess relapse.

Expected results

Rimonabant may increase striatal dopamine D₂ receptor availability in abstinent cocaine users compared to controls. We expect to find a reduced craving for cocaine and/or impulsivity in participants who receive rimonabant compared to those who receive placebo. If the previous results occur, we expect to find attenuated relapse in cocaine users, as assessed by urine benzoyllecgonine tests.

Discussion

With good outcomes of this clinical study, rimonabant may be very helpful as a new medication for better treatment outcomes in preventing relapse in detoxified cocaine abusers.

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TITLE
BRAIN ACTIVATION PRECEDING THE EXPERIENCE OF AUDITORY VERBAL HALLUCINATIONS

AUTHORS

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ABSTRACT

Introduction

Previous studies indicated a network of regions significantly activated during auditory verbal hallucinations (AVH). How this network is triggered, however, remains elusive. Brain regions showing significant signal changes preceding AVH might reveal its pathophysiological substrate.

Methods

Fifteen schizophrenia-spectrum patients indicated presence of AVH during 3T PRESTO SENSE fMRI scanning by squeezing a small hand-held balloon. To control for motor related activation fifteen control subjects squeezed this balloon at random time intervals. The Finite Impulse Response was used as the basis function to enable analysis of brain activation 6-0 seconds prior to the AVH and balloon-squeezes.

Results

Prominent deactivation preceding AVH was observed in the left parahippocampal gyrus. In addition, significant deactivation was found in the left superior temporal, right inferior frontal and left middle frontal gyri as well as in the right insula and left cerebellum. No significant signal changes were revealed prior to the balloon-squeezing in the control subjects.

Conclusions

Negative signal changes in the parahippocampal gyrus have been associated with memory retrieval. This may imply that retrieval from memory triggers AVH, subsequently activating cortical regions leading to the experience of AVH

KEY WORDS

Auditory verbal hallucinations, language, fMRI, trigger, Finite Impulse Response

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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 large 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 MS lesion formation. We have investigated alterations in the rheostat in different MS lesion types by immunohistochemical analysis. Our results demonstrate an altered sphingolipid rheostat in MS tissue which is most prominent in astrocytes. Identifying affected cell types and understanding the molecular mechanisms that regulate lesion formation is crucial for identifying new targets that limit MS lesion formation and progression.

KEY WORDS

Sphingolipids, ceramide, S1P, Multiple Sclerosis, astrocyte, MS lesions

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TITLE**INTRACELLULAR MECHANISMS UNDERLYING RATE AND TEMPORAL TUNING TO SINUSOIDAL AMPLITUDE MODULATED TONES IN THE MOUSE INFERIOR COLLICULUS****AUTHORS**Hans-Rüdiger Geis, J.G.G. Borst**DEPARTMENT/INSTITUTE**

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ABSTRACT

Changes in temporal envelope are important defining features of natural acoustic signals. Many cells in the inferior colliculus (IC) respond preferentially to certain modulation frequencies, but how they accomplish this is not yet clear. We therefore recorded intracellular responses in the IC of anesthetized mice while presenting sinusoidal amplitude modulated tones. The relation between number of spikes and modulation frequency was used to construct rate modulation transfer functions (rMTFs). We observed different types of rate tuning, including band-pass (16%), band-reject (13%), high-pass (6%) and low-pass (6%) tuning. In the high-pass rMTF neurons and some of the low-pass rMTF neurons the tuning characteristics appeared to be already present in the inputs. Both in band-pass and band-reject rMTF neurons the non-linear relation between membrane potential and spike probability ensured preferential spiking during only a small part of the modulation period. Band-pass rMTF neurons received rapidly rising EPSPs, allowing good phase-locking to brief tones and intermediate modulation frequencies. At low modulation frequencies, adaptation of their spike threshold contributed to the onset response. In contrast, band-reject rMTF neurons responded with small EPSPs or IPSPs to brief tones. In these cells, a power law could describe the supralinear relation between average membrane potential and spike rate. Differences in timing of synaptic input and presence or absence of spike adaptation therefore define the two most common classes of rate-tuned cells in the mouse IC.

KEY WORDS

Rate-tuning, midbrain, in vivo patch-clamp

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TITLE**SPECIFIC INTERACTION OF THE PRIMING FACTOR DOC2B WITH PIP₂****AUTHORS**Asiya Giniatullina, Sascha Martens, Matthijs Verhage, Sander Groffen**DEPARTMENT/INSTITUTE**

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ABSTRACT

Fast synaptic vesicle release requires the binding of Ca²⁺ ions to the C2 domains of synaptotagmin. The synaptic protein DOC2B contains two C2 domains with high similarity to synaptotagmin (C2A and C2B), that function as Ca²⁺-dependent phospholipid binding modules. In contrast to synaptotagmin, DOC2B is cytosolic and is recruited to the plasma membrane by calcium elevation. DOC2B has the property to enhance the secretory capacity of neuroendocrine cells. The aim was to show how, through DOC2, calcium and phospholipids play an important role in regulating stimulated secretion. We used two independent methods to study the properties of DOC2 binding to membranes: kinetic liposome aggregation assays and lipid cosedimentation assays. The results indicate that both the C2A and C2B domain of DOC2B present Ca²⁺-dependent phospholipid binding. The Ca²⁺-dependent liposome aggregation requires the anionic lipid phosphatidylserine. Presence of 2% phosphoinositol-4,5-bisphosphate (PIP₂) allows Ca²⁺-independent liposome aggregation, and also enhances the Ca²⁺-dependent binding to phosphatidylserine. The interactions of DOC2 proteins with lipid membranes are of interest to understand how DOC2B regulates synaptic secretion and may also apply to other proteins containing C2 domains.

KEY WORDSCalcium, DOC2, C2 domains, PIP₂, phospholipids**TELEPHONE-NUMBER:** 020-5987792**E-MAIL-ADDRESS:** asiya.giniatullina@cncr.vu.nl

TITLE**PLASTICITY AND FUNCTIONAL MICRO-ORGANIZATION OF CROSS-MODAL INTERACTIONS IN THE MOUSE VISUAL CORTEX****AUTHORS**

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ABSTRACT**Introduction**

The primary sensory cortices are generally thought to be neural structures specialized in the processing of sensory input from a single modality. Surprisingly, some recent studies indicate that neurons, or networks of neurons, within these sensory cortices can additionally be modulated by stimuli from different modalities. These cross-modal influences can originate from other sensory modalities and from higher order cognitive modalities like a reinforcement or emotional signal. From a conceptual point of view, the presence of direct cross-modal influences in the sensory cortices could help sensory networks to place the dominant uni-modal input into a bigger multi-sensory context.

Question

In the present study we will investigate the functional micro-organization and network plasticity of cross-modal modulations in the primary visual cortex.

Methods

By using two-photon laser scanning microscopy in combination with multi-cell bolus loading of a fluorescent intracellular calcium indicator, we defined single neuron and network coding of stimuli from different modalities.

Results so far

The current data show the functional micro-organization of single neuron receptive fields in the primary visual cortex.

Conclusions so far

Calcium imaging can be used to provide a reliable description of single neuron and network coding in the superficial layers of the cortex.

KEY WORDS

Calcium imaging, reinforcement learning, cross-modal interactions, sensory integration, primary visual cortex, mouse, two-photon laser scanning microscopy.

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TITLE

FROM BEHAVIOR TO AMPA RECEPTORS AND BACK: NEUROADAPTIVE CHANGES IN THE RAT PREFRONTAL CORTEX IMPLICATED IN VULNERABILITY TO RELAPSE TO HEROIN SEEKING

AUTHOR(S)

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ABSTRACT

Relapse to heroin addiction can occur even after a long period of abstinence and is usually caused by re-exposure to otherwise neutral environmental stimuli (or cues) which were previously learned to be associated with heroin taking. In recent years, it has become clear that these behavioral abnormalities are paralleled by persistent alterations in the neuronal circuitry involved in motivation and reward processing. However, it is unknown whether re-exposure to the heroin-conditioned cues alone can induce acute synaptic changes, and whether prevention of these changes can reduce relapse behavior. We studied acute neuroadaptations that take place immediately following re-exposure to drug-conditioned cues in medial prefrontal cortex (mPFC), an area exerting cognitive control of behavior. We used a combination of molecular, behavioral and physiological techniques to reveal a link between the internalization of AMPA receptor in mPFC and relapse to drug-seeking. We found that decrease in expression of AMPA receptors in the mPFC and decrease in synaptic strength in mPFC pyramidal neurons accompany relapse caused by heroin-conditioned cue presentation. We also show that pharmacological interference with AMPA receptor endocytosis can reduce relapse behavior.

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TITLE**ANTICIPATORY GRIP FORCE CONTROL USING A CEREBELLAR MODEL****AUTHORS**Jornt R. de Gruijl, P. van der Smagt, C.I. de Zeeuw**DEPARTMENT/INSTITUTE**

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ABSTRACT

Grip force modulation has a rich history of research, but remains to be investigated at the neural level and applied in a robotic system. Adaptive grip force control as exhibited by humans would enable robots to handle objects with sufficient yet minimal force, thus minimizing the risk of crushing objects or inadvertently dropping them. We investigated the feasibility of grip force control by means of a biological neural approach to ascertain the possibilities for future application in robotics. As the cerebellum appears crucial for adequate grip force control, we tested a computational model of the olivo-cerebellar system. This model takes into account that the processing of sensory signals introduces a 100 ms delay, and because of this delay, the system needs to learn anticipatory rather than feedback control. For training, we considered three scenarios for feedback information: (1) grip force error estimation, (2) sensory input on deformation of the finger tips, and (3) as a control, noise. The system was trained on a data set consisting of force and acceleration recordings from human test subjects. Our results show that the cerebellar model is capable of learning and performing anticipatory grip force control closely resembling that of human test subjects despite the delay. The system performs best if the delayed feedback signal carries an error estimation, but it can also perform well when sensory data are used instead. Thus, these tests indicate that a cerebellar neural network can indeed serve well in anticipatory grip force control not only in a biological but also in an artificial system.

KEY WORDS

Cerebellum, timing, grip force, simulation, computer model, neural network

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TITLE**AUTOMATED DETECTION OF COMPULSIVE CHECKING BEHAVIOR IN RATS****AUTHORS**

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ABSTRACT

Obsessive compulsive disorder (OCD) is a psychiatric disorder with a life-time prevalence of 2-3%. Patients suffer from strong obsessive thoughts and perform rituals (compulsions) to get in control of these obsessions. OCD rituals vary from “washing behavior” to “checking behavior” or “counting”. Of course checking can be a normal behavior, but OCD patients perform these rituals so excessively that it interferes with their normal daily functioning. Currently, selective serotonin reuptake inhibitors (SSRI's) are the most effective treatment for OCD patients, but still 30-40% does not respond to this medication.

Pre-clinical research with valid animal models for OCD is necessary to gain more insight in the pathogenesis of OCD and to discover new therapies. At this point there are no well validated OCD animal models available. Szechtman et al. have preformed research on a candidate animal model in which quinpirole sensitized rats develop compulsive checking behavior. The aim of this study is to investigate the compulsive behavior in this model in more detail and evaluate the potential use of Theme for automated detection of behavioral patterns in this animal model.

In this model rats are injected twice a week with the dopamine D₂/D₃ receptor agonist quinpirole 0.5 mg/kg for 5 weeks. After each injection, the animal is placed on a large open field (160X160 cm) with 4 objects and is tracked for 60 min with EthoVision. The EthoVision data is fed into the software package Theme (Noldus Information Technology, The Netherlands) which is a tool for pattern detection and analysis in time-based data. Data analysis in Theme results in a set of hierarchical time patterns, also called T patterns, for individual animals at different time points (sessions). Using behavioral pattern analyses we found that quinpirole treated rats had a smaller repertoire of patterns, which were simpler, shorter in duration and were preformed more frequently compared to the saline group.

These results revealed the behavioral characteristics of very simple and purposeful behaviors that are repeated very frequently and this resemble the behavior in patients with OCD and confirm the validity of this pharmacological model for OCD for this condition. We can conclude that T pattern analysis is a useful tool in the development of an animal model for compulsive behavior. It not only adds a valuable measurement, but also provides a new dimension in the behavioral data that translates to OCD.

KEY WORDS

Obsessive compulsive disorder, behavioural pattern analysis, theme

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TITLE**MATERNAL CARE INFLUENCES FUNCTION AND MORPHOLOGY IN THE ADULT RAT HIPPOCAMPUS IN A SEX-DEPENDENT MANNER****AUTHORS**

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ABSTRACT

In humans, early life adversity has been associated with an increased risk for adult psychopathology, but a functional link has yet to be found. To gain more insight into how environmental events in early life can alter limbic brain function and structure we extensively investigated hippocampal areas CA1 and dentate gyrus (DG) of adult rats that received varying amounts of maternal care.

In rats, the amount of maternal care provided to the pups in the first postnatal week varies between litters, and mothers can be classified as either High, Mid or Low caring. In this model, early experience has already been found to alter neuroendocrine function and glucocorticoid receptor expression levels in several brain regions. Additionally, we found that the degree of long-term potentiation (LTP) and the morphology in the adult hippocampus differed significantly between offspring of High and Low caring mothers.

Currently, we are using a more refined maternal care model, in which we determine the amount of maternal care that each *individual* pup within a litter receives in the first postnatal week.

In Long-Evans rats, we found a considerable variation in the amount of licking and grooming (LG) the mother provides to each of her pups. Interestingly, it appeared that overall, male pups were significantly more attended to than female pups. Based on litter means, we classified the pups (both male and female) as High, Mid or Low care receiving offspring.

Preliminary results indicate that in *males* the same functional differences between High and Low pups *within* litters are seen as earlier found in pups *between* High and Low litters. Thus, so far a positive correlation between the amount of LG received and the degree of LTP is seen in both the CA1 and DG when corticosteroid levels are low. This correlation disappeared or was even inversed when the slices were incubated with corticosterone at the time of LTP-induction.

In *female* DG we found the same correlations between amount of LG and degree of LTP as in males, both in conditions with and without the presence of corticosterone. Interestingly however, in the CA1, we found *opposite* correlations. Also, female neurogenesis and dendritic morphology data seem so show an inversed pattern compared to what was found earlier in males in the original maternal care model. Analysis of male hippocampal morphology in pups subjected to the new model is currently in process.

Further research will look into methylation patterns of several genes related to neurogenesis, spinogenesis, dendritic outgrowth, LTP and corticosterone response.

KEYWORDS:

Maternal care, corticosterone, long-term potentiation, morphology, neurogenesis

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TITLE**STUDY TO ELUCIDATE NEOGENIN SIGNALLING AND ITS ROLE IN AXON GUIDANCE****AUTHORS**

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ABSTRACT

Neogenin is a key regulator of several important processes in the developing brain. It is a transmembrane receptor that is known to be implicated in axon guidance, neuronal differentiation, morphogenesis and cell death. Neogenin is a member of the Deleted in Colorectal Cancer (DCC) family of Netrin receptors and can bind members of two different ligand families: the Netrins and the Repulsive Guidance Molecules (RGMs). This study focuses on the role of RGMA-Neogenin signalling in axon guidance. Axon guidance is an important process during development that regulates the directed growth of axons to their target areas in the brain. Impaired axon guidance may underlie several different neural disorders including epilepsy, schizophrenia and autism. Netrins and RGMs have opposing effects on growing axons expressing Neogenin. Netrin-1 binding to Neogenin has an attractive effect on axon growth, while binding of RGMA induces axon repulsion. In this study several techniques are used to characterize brain structures and axon tracts that are dependent on RGMA/Neogenin signalling for proper development. RNA in situ hybridisation, RGMA-AP section binding and immunostaining techniques are employed to show that RGMA and Neogenin are involved in the development of the fasciculus retroflexus tract, an axon tract composed of axons growing from the habenula to the interpeduncular nucleus. Future research employing functional in vitro and in vivo assays will reveal the functional aspects of RGMA-Neogenin signalling in the development of this and other axon tracts. A second part of this study describes the generation of transgenic mice that express a GFP-Neogenin fusion construct that will be used to identify Neogenin binding partners that play a role in Neogenin signalling. At the moment there is very little knowledge of neuronal Neogenin. The small GTPase RhoA and its effector Rho-kinase are known to be activated by RGMA binding to Neogenin, however the exact mechanism is unknown. Immunoprecipitation experiments on brain lysates of GFP-Neogenin mice will reveal new binding partners of Neogenin. In all, this research will contribute to a better understanding of Neogenin function in the brain.

KEY WORDS

Neogenin, RGMA, axon guidance, development, signalling

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TITLE**IDENTIFYING THE SPECIFIC ROLE OF TRANSCRIPTION FACTORS *LMX1A* AND *LMX1B* IN THE GENETIC CASCADE LEADING TO MESODIENCEPHALIC DOPAMINERGIC NEURONS****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). A 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*. Both are required to trigger differentiation into mdDA neurons, and are expressed in overlapping fields in DA cell progenitors, early in the molecular program. 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 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 ES-cells. *Lmx1b* has, in contrast to *Lmx1a*, a much broader expression field. To investigate how these factors are exactly involved in mdDA development and maintenance, we first have to identify the 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.

KEY WORDSMeso-diencephalic dopaminergic neurons, neuronal development, transcriptional profile, transcription factors *Lmx1a* and *Lmx1b***TELEPHONE-NUMBER:** 088 -7568828**E-MAIL-ADDRESS:** e.j.hoekstra@umcutrecht.nl

TITLE
HOW COMPLEMENT PROTEIN C6 DEFICIENCY AFFECTS EPILEPTOGENESIS

AUTHORS

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ABSTRACT

Previous studies have suggested that inflammation can play a crucial role in the development of temporal lobe epilepsy (epileptogenesis). One of these inflammatory pathways, the classical complement cascade is particularly activated during the latent period before epilepsy becomes manifest. Activation of this pathway leads to the formation of the membrane attack complex (MAC; consisting of C6, C7, C8 and C9 proteins) which forms a membrane pore that eventually causes cell lysis. To study whether activation of MAC could be involved in the development of epilepsy, we used the kindling model for temporal lobe epilepsy in complement protein C6 deficient and wild type rats. Absence of the formation of MAC, via C6 deficiency, is expected to reduce inflammation and epileptogenesis. In the kindling model, daily applied electrical subconvulsive stimuli initially generate focal seizures, but over time the same stimulus generates generalized seizures. In C6 deficient rats, seizure duration did not differ from WT rats. However, the development from focal to generalized seizures was delayed in comparison to WT rats. All rats ultimately exhibited generalized seizures after 25 stimulations. The results suggest that absence of MAC formation can delay but not prevent seizure spread to other brain regions.

KEY WORDS

Epilepsy, epileptogenesis, neuroinflammation, complement

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TITLE
THE ROLE OF ARC EXPRESSION IN THE SPINAL CORD.

AUTHORS

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ABSTRACT

Activity regulated cytoskeleton associated protein (Arc/Arg3.1) is present in several forebrain areas, where it is involved in various aspects of synaptic plasticity, including long term potentiation (LTP) and memory consolidation. It has been shown that Arc/Arg3.1 is transported to activated synapses in dendrites. Therefore Arc/Arg3.1 also has been used as an activity dependant neuronal marker. Studies on the physiological function of Arc/Arg3.1 have shown that it is involved in regulating AMPA receptor trafficking by endocytosis. In this study it is determined whether Arc/Arg3.1 is also involved in synaptic plasticity that is known to occur in the spinal dorsal horn after peripheral nociceptive stimulation. We first investigated the expression of Arc/Arg3.1 mRNA in the rat spinal dorsal horn after various peripheral nociceptive stimuli. Arc/Arg3.1 mRNA expression was investigated after acute pain stimulation and chronic inflammatory pain. To further characterize the Arc/Arg3.1 expressing neurons, in situ hybridization for Arc/Arg3.1 mRNA was combined with immunohistochemistry for colocalization with other markers. To investigate the role of Arc in pain behavior the mechanical and thermal thresholds were assessed in Arc^{-/-} mice. These thresholds were also investigated during acute and chronic pain that was applied to Arc^{-/-} and wild-type mice.

KEY WORDS

ARC, spinal, pain, central sensitization

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TITLE**DISSOCIATING THE “RETRIEVAL SUCCESS” REGIONS OF THE BRAIN: EFFECTS OF RETRIEVAL DELAY****AUTHORS**Willem Huijbers, C.M.A. Pennartz, S.M. Daselaar**DEPARTMENT/INSTITUTE**

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ABSTRACT

A small group of brain areas has been strongly linked to episodic long-term memory (LTM) retrieval, the conscious remembering of past events. Besides the medial temporal lobe, these regions include medial prefrontal, posterior parietal (PPC) and posterior midline regions (PMR). Anatomically, these areas overlap with the so-called “default mode network” (DMN), which consistently shows deactivation during effortful task performance. Given that successful retrieval decisions are less demanding than unsuccessful decisions, this raises the question whether DMN activity during memory tasks truly reflects episodic LTM or merely a difference in task difficulty. In order to address this important issue, we manipulated retrieval delays within the context of a continuous recognition task during fMRI scanning. We assumed that recognition responses after short delays are very easy but rely primarily on short-term memory, whereas responses after longer delays are more difficult but rely exclusively on episodic LTM. Behavioral results confirmed that longer delays were more difficult. Moreover, the fMRI results indicated several functional dissociations associated with short and long delays within different retrieval success regions. Most importantly, within PPC, we found a double dissociation between dorsal and ventral areas, and within PMR we found a triple dissociation between the precuneus, posterior cingulate, and retrosplenial cortex. These findings not only shed more light on the neural correlates of episodic memory, but also on the functional roles of different DMN regions.

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TITLE**VISUALIZING SYNAPTIC HETEROGENEITY IN AUTAPTIC NEURONS****AUTHORS**

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ABSTRACT

Communication between neurons is mediated by synapses, where electric activity is translated into a chemical signal, i.e. the fusion of neurotransmitter-filled vesicles with the plasma membrane. Synaptic transmission is a probabilistic process in the central nervous system (CNS); typically about 40% of the action potentials arriving at a synapse actually triggers the fusion of a synaptic vesicle. Moreover, presynaptic terminals originating from the same neuron may vary substantially in their probability of transmitter release, although the degree of heterogeneity depends on the class of neurons. The release probability at an individual synapse can vary over time, depending on the pattern of neuronal activity, modulation of presynaptic excitability and the exact makeup of the vesicle fusion machinery at a given synapse. In this way, synapses are actively involved in processing and storing information in neuronal circuits. To study the biochemical nature of synaptic heterogeneity, we made use of the fluorescent reporter syphY to visualize individual fusion events at synapses of cultured autaptic neurons. By using this technique, we are able to determine the release characteristics of all individual synapses of a single neuron. Not only can we determine their release probability at single action potentials, it is also possible to observe changes in synaptic release behavior over time, during different short-term plasticity protocols or pharmacological treatments. Simultaneous patch clamp electrophysiology recordings are used to correlate changes in presynaptic activity with alterations in the postsynaptic response. This experimental design can be used to determine the role of vesicle fusion proteins, presynaptic receptors and intracellular signal molecules in defining and modulating synaptic heterogeneity.

KEY WORDS

Vesicle release, fluorescence microscopy, synaptic heterogeneity

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TITLE

RELATING GENE EXPRESSION NETWORK RESULTS TO BEHAVIORAL PHENOTYPES IN A CHROMOSOME SUBSTITUTION STRAIN F2 POPULATION IN ORDER TO IDENTIFY A GENE UNDERLYING A QTL

AUTHORS

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ABSTRACT

The covariance between gene expression networks in the brain and behavior is an important approach to further unravel the determinants of neurobehavioral traits. The recent advances in mouse genetic mapping strategies and automated home cage behavioral registration that aim to identify validated pre-clinical models for psychiatric disorders (Kas et al., 2008) pave new roads to determine genetic pathways for these complex disorders. Behavioral tests in different strains of mice are used to unravel the genetic causes of neuropsychiatric disorders. A chromosome substitution panel is very efficient in screening the genome systematically for phenotypes of interest (Singer et al., 2004).

In an earlier study, a panel of chromosome substitution strains (CSS), were screened in a automated home cage environment to efficiently identify QTL-intervals for anxiety-related behaviors. This automated behavioral set-up enables multi day recordings without experimenter interference. The females of the CSS15 line showed increased avoidance behavior. A F2 population was generated and a quantitative trait locus (QTL) on chromosome 15 was determined (de Mooij – van Malsen et al., in preparation).

In order to refine the QTL and identify the gene underlying the quantitative trait, we set out to incorporate whole genome gene expression data obtained from hippocampal tissue from this F2 population. This data was analyzed using a weighted gene co-expression method (Zhang et al., 2005). Clustering was performed on genes to create networks of co-expressed genes. This in turn resulted in reconstruction of a limited number of groups of genes (“modules”) with highly similar expression profiles. The most connected genes in the network are driving the modules and are considered to be most important. In this study we identified modules that were correlated with the behavioral measures. Highly connected genes on chromosome 15 within the QTL peak that was found earlier were considered to be candidates.

Several genes in this region were found to be important genes within modules related to the behavioral parameters and deserve further investigation. Especially Kifc2 and Dgat1 were interesting candidates since they are suggested to be involved in neuronal processes and influence behavior. In order to fine map the behavioral QTL genotypes for these genes were determined and will added to the analyses. Results of this study will aid in discovering genes influencing behavior by combining information about genotype, gene expression and behavioral measures.

KEY WORDS

Mouse model, anxiety, avoidance, home cage, gene expression, networks, QTL, behavior

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TITLE
THERAPEUTIC EFFICACY OF PHYSOSTIGMINE AND OBIDOXIME IN A SOMAN-POISONED GUINEA PIG MODEL

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ABSTRACT

Organophosphates (OPs), such as the nerve agent soman, irreversibly inhibit acetylcholinesterase (AChE) activity, resulting in excessive buildup of ACh concentrations in cholinergic synapses. The following hyperactivation of the ACh receptors causes a variety of toxic effects like hypersecretions, seizures, respiratory distress and ultimately death. To date, treatment of organophosphate poisoning consists of antagonizing effects of excess ACh by anticholinergics, reactivation of AChE by oximes and attenuation of seizures by diazepam. However, seizures induced by severe poisoning are difficult to manage and different OPs require different oximes for reactivation, rendering the current treatment insufficient. Identification of alternative treatment targets in OP poisoning might enable treatment optimization.

In the present study, effects of different doses of soman on the development of clinical signs, EEG, heart rate, respiration and AChE activity in blood and brain were measured in the guinea pig to establish a model dose. This approach showed that 30 ug/kg of soman induced >99% of AChE inhibition within 10 minutes, bronchoconstriction and seizure development for at least 90 minutes, after which the experiment was terminated.

In this model, the effects of obidoxime (AChE reactivator) and physostigmine (reversible AChE inhibitor) and their combination were investigated in the soman poisoned guinea pig. Both physostigmine and obidoxime, injected 1 minute after soman, improved the outcome on most parameters. Obidoxime protected a very small fraction of AChE activity but not against seizure development, whereas physostigmine treatment preserved a greater AChE fraction and prevented the development of seizures in most, but not all, animals. Administration of both drugs as a combination after soman, shortened seizure duration to approximately 10-15 minutes, which was not reflected by differences in AChE activity.

In conclusion, a soman-poisoned guinea pig model was established, which provides a valuable tool to identify alternative treatment targets at both biochemical and physiological level. The present results confirm that protection of AChE after OP poisoning provides a major contribution to treatment efficacy. Other pathways will be investigated in a future study.

KEY WORDS

Organophosphate poisoning, acetylcholinesterase, guinea pig, physostigmine, EEG

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TITLE**EPILEPTOGENIC CHANGES IN A JUVENILE MODEL OF TEMPORAL LOBE EPILEPSY****AUTHORS**

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ABSTRACT

Temporal Lobe Epilepsy (TLE) is one of the most common focal epilepsy syndromes. Approximately 25% of patients suffering from this disease develop a resistance to all anti-epileptic drugs. TLE has a typical disease course which involves an "initial precipitating event" followed by a latent phase in which no clinical signs of epilepsy are present yet. Molecular changes are occurring in this phase however and these can subsequently lead to the development of epilepsy. This process of epileptogenesis has been the focus of this study. Hippocampal tissue obtained during surgery to treat TLE has given us clues about changes due to epileptogenesis at the chronic phase of the disease. For instance gene expression studies of this material have shown that parts of innate immune system and the glutamine-glutamate cycle differ greatly between patients and controls. Marked changes in the immune system were seen in the chemokine CCL4 and its receptor CCR5. Also the key glial enzyme of the glutamate-glutamine cycle, glutamine synthetase (GS) was shown to be down regulated in TLE patients. The aim of this study was to determine the expression change of these proteins during epileptogenesis.

Therefore we used the juvenile rat lithium pilocarpine model (LiPC) for epilepsy. This is an established model for TLE with the same disease course as seen in humans. It involves giving a lithium injection at postnatal day 20 (p20) and inducing status epilepticus with pilocarpine at p21. Experimental and control animals were sacrificed at different time points after the SE induction, namely 2, 4 and 8 weeks (latent phase) and 19 weeks (chronic or epileptic phase). Subsequently the brains were embedded in paraffin and cut into 7 um sections for immunohistochemical analysis of CCL4, CCR5, Vimentin (reactive glial marker) and GS. Immunoreactivity was quantified using Image J.

CCL4 and CCR5 expression was found to be significantly up regulated at all time points. This expression was found mainly in the amygdal regions and the hilus of the hippocampus. Control animals, as expected, did not show any expression of these proteins as the normal brain is usually deprived of immune activity. The marker for reactive microglia vimentin was also up regulated in the hilar region of the hippocampus, yet this up regulation was only found at 2 and 4 weeks. GS expression was only significantly decreased in the hilus of the hippocampus at 8 and 19 weeks. These results show in the critical epileptogenic time a marked increase of immune components CCL4 and CCR5. This increase in expression is partly in the same region as vimentin (the hilus) suggesting a relationship with reactive microglia. Additionally, the hilus is the region where in the human TLE brain, and in the final two time points of our animal model, a marked decrease is seen in the expression of GS.

Our results confirm the changes seen in TLE patients and suggest that specific components of the immune system, such as CCL4 and CCR5, and the reduction in GS are not simply a result of seizure activity and may play a role in epileptogenesis.

KEY WORDS

Temporal lobe epilepsy, immune system, glutamate, lithium/pilocarpine

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TITLE**QUANTITATIVE SYNAPTIC PROTEOMICS IN A MOUSE MODEL FOR THE FRAGILE X SYNDROME REVEALS MOLECULAR CHANGES UNDERLYING NEUROTRANSMISSION AND SYNAPSE MORPHOLOGY****AUTHORS**

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ABSTRACT

Fragile X syndrome (FXS) is the most frequently form of hereditary mental retardation. FXS results from abnormally large size of the CGG repeat (>200) at the 5'-untranslated region of the X-linked *fmr-1* gene and leads to reduced expression of Fragile X Mental Retardation Protein (FMRP). FMRP is an mRNA binding protein regulating transport and translation of synaptic mRNAs. The deficit of FMRP expression is associated with an appearance of immature synapses with long and thin spines; synaptic plasticity is generally diminished.

Here, we use a quantitative proteomics approach in an FXS mouse model to reveal global changes in hippocampal synapse protein constituents. We used 8 independent biological replicates. The peptides derived from the trypsin digested proteins were labeled with 8-plex iTRAQ reagents for quantitative analysis. The 2D LC-tandem mass spectrometry identified about 700 proteins, from which about 400 proteins were quantified. A distinct functional group of proteins was strongly regulated, including MARCKS, BASP-1, GAP-43, BM88 and neurogranin that all are known to play important roles in lamellapodia outgrowth and cell differentiation. Their up-regulation may underlie the observed aberrant synapse morphology. In addition, proteins involved in synaptic vesicle release were up-regulated, albeit at a lower level. In accordance, pair-pulsed facilitation analysis showed subtle differences in transmitter release between mutant and wild type mice.

At present, we study the synaptic protein interactome, focusing on proteins that are regulated in the *Fmr-1* knockout mice, in order to gain better insight into the molecular mechanisms of FXS. We have immuno-isolated the GAP-43 protein complex, and showed the presence of diverse protein classes in this complex, which include pre-synaptic and Ca²⁺ dependent proteins. The structural interaction of GAP-43 and pre-synaptic proteins reflects the increase of both classes of proteins in the synapse of the FXS mouse model.

KEY WORDS

Fragile X, hippocampus, synapse, proteomics

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TITLE**METHOD DEVELOPMENT STUDIES FOR REPEATEDLY MEASURING ANXIOLYTIC DRUG EFFECTS IN HEALTHY HUMANS****AUTHORS**

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ABSTRACT

Human experimental models for anxiety may serve as translational tools for translating preclinical psychopharmacological investigations into human studies. For the evaluation of drugs of which pharmacokinetics and -dynamics are unidentified, repeating measurements after drug administration is necessary for characterizing the time course of drug effects. In experiment 1, a threat-of-shock paradigm and adaptations of the Trier mental arithmetic test and the Stroop colour naming test were repeated 4 times within a day to evaluate whether anxiety responses to this test battery remain stable after repeated testing. This procedure was repeated on 4 days in a second experiment to evaluate suitability of the paradigm for a crossover design with multiple sessions. Results indicate no reductions or changes in fear potentiated startle, the main outcome measure for the threat paradigm, over test sessions or days. Skin conductance responses and subjective ratings under threat of shock showed significant fluctuations, but also no systematic decline over time. Finally, the threat paradigm and Stroop test resulted in small increases in reported state anxiety while mental arithmetic produced larger effects that diminished after the first test day. It is concluded that especially the startle paradigm could be a useful new instrument for screening new anxiolytic drugs.

KEY WORDS

Startle reflex, anxiety, fear, skin conductance response, experimental model

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TITLE**ABUNDANT EXTRACELLULAR MYELIN IN THE MENINGES OF PATIENTS WITH MULTIPLE SCLEROSIS****AUTHORS**

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ABSTRACT

In multiple sclerosis (MS) myelin debris has been observed within MS lesions, in cerebrospinal fluid and cervical lymph nodes, but the route of myelin transport out of the brain is unknown. Drainage of interstitial fluid from the brain parenchyma involves the perivascular spaces and leptomeninges, but the presence of myelin debris in these compartments has not been described.

Aims

To determine whether myelin products are present in the meninges and perivascular spaces of MS patients.

Methods

Formalin-fixed brain tissue containing meninges from 29 MS patients, 9 non-neurological controls, 6 Alzheimer's disease, 5 stroke, 5 meningitis and 7 leukodystrophy patients was investigated, and immunohistochemically stained for several myelin proteins (PLP, MBP, MOG and CNPase). On brain material from MS patients and (non-)neurological controls, PLP immunostainings were used to systematically investigate the presence of myelin debris in the meninges, using a semi-quantitative scale.

Results

Extensive extracellular presence of myelin particles, positive for PLP, MBP, MOG and CNPase in the leptomeninges of MS patients was observed. Myelin particles were also observed in perivascular spaces of MS patients. Immunohistochemical double-labelling for macrophage and dendritic cell markers and PLP confirmed that the vast majority of myelin particles were located extracellularly. Extracellular myelin particles were virtually absent in meningeal tissue of non-neurological controls, Alzheimer's disease, stroke, meningitis and leukodystrophy cases.

Conclusions

In MS leptomeninges and perivascular spaces, abundant extracellular myelin can be found, whereas this is not the case for controls and other neurological disease. This may be relevant for understanding sustained immunogenicity or, alternatively, tolerogenicity in MS.

KEY WORDS

Multiple sclerosis, myelin, meninges, extracellular

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TITLE
SELECTING AND VALIDATING GENE TARGETS IMPLICATED IN PARKINSON'S DISEASE DEVELOPMENT AND PROGRESSION

AUTHORS

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disease with, in most cases, an unknown etiology. Although there are some indications of the role of oxidative stress and α -synuclein protein aggregation as the initiators of neuronal death, our understanding of the causes of neurodegeneration of dopaminergic (DA) neurons in PD is far from complete. The main aim of this study is to further validate dysregulated genes identified in a microarray study on human PD and matched control post mortem tissue (Bossers et al, 2008), and to examine their role in both disease development as well as its progression. Currently we are selecting genes of interest and localizing their presence in human PD and control substantia nigra with the help of immunohistochemistry and *in situ* hybridization. Functional characterization and validation of targets will be performed on the human SH-SY5Y cell line. These cells develop a dopaminergic phenotype upon differentiation with retinoic acid and can be used as an *in vitro* model for degeneration of DA-neurons through treatment with the toxin 1-methyl-4-phenyl-2,3-dihydropyridinium ion (MPP+). In two pilot experiments we determined the best conditions in which cells can be cultured for a long term in combination with MPP+ treatment. We designed and performed a microarray study to characterize the molecular phenotype of these cells after differentiation and MPP+ toxicity and compared these data to the human microarray data. Furthermore, with this model, we will perform a high-content cellular screening of selected genes of interest and determine their role in the context of PD. We intend to follow-up this work *in vivo* where, depending on the function of the selected gene, we aim to either rescue DA-neurons or show a role for a particular target in DA-neuron degeneration with the use of AAV vector technology.

Reference

Bossers *et al.*, 2008, Brain Pathology, in press.

KEY WORDS

Parkinson's disease, gene profiling, MPP+ toxicity, SH SY5Y cells

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TITLE
SUBCELLULAR LOCALISATION OF NEUROBEACHIN

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ABSTRACT

Neurobeachin (nbea) is a gene encoding a brain-enriched putative A-kinase adaptor protein (AKAP) and is a candidate gene for autism. Neurobeachin-null mice die at birth due to secretion defects at the neuromuscular junction producing a failure to breath. Nbea is a multi-domain protein containing a number of distinct domains, i.e. PKA RII binding-domain, a C-terminal WD40 repeat, a Beach domain and a Pleckstrin homology-like domain. The role of the full-length nbea, as well as its specific domains, in cellular function was determined by overexpression of truncated and full-length forms of nbea in both wild-type and nbea-null background cultured hippocampal neurons. No colocalization of endogenous nbea with synapsin, VAMP or PSD-95 could be found in the dendrites of wild-type neurons, while cases of close apposition of nbea and synapsin were found in the axon. The overexpression of the Beach domain only, Pleckstrin homology domain together with the Beach domain and the truncated form containing the C-terminal region of nbea do not colocalize with the endogenous nbea. The above results suggest that nbea might be involved in trafficking. However, further studies will be necessary to confirm this notion.

KEY WORDS

Neurobeachin, AKAP, BEACH

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TITLE
SLEEP PROMOTES INSTRUMENTAL LEARNING IN RATS

AUTHORS

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ABSTRACT

In instrumental learning (IL) a subject acquires the knowledge that an action results in a wanted outcome. For instance, when rats learn to press a lever to obtain a reward they learn about the contingency of action and outcome and about the outcome as a wanted goal, ie they acquire goal-directed behavior.

In a previous study of our group, rapidly learning rats that showed a clear session-to-session improvement had a stronger increase in dopamine (DA) efflux in the nucleus accumbens compared to slowly learning rats (Cheng & Feenstra, 2006). As both DA and sleep have been shown to be involved in consolidation of learning (Dalley et al, 2005; Stickgold, 2005), we became interested in sleep between the two sessions. Therefore we tested whether the amount of sleep is related to improvement in IL and whether sleep deprivation would block such an effect.

Male Wistar rats were given two daily sessions of IL during the active (dark) phase of the light-dark cycle. One lever was presented to the rat in 30 discrete trials. Pressing the lever resulted in the delivery of one pellet. Sleep deprivation in between the sessions using mild forced locomotion completely blocked any session-to-session improvement and resulted in a higher number of sessions needed to reach the learning criterium of > 90% responses.

Before and between IL-sessions, EEG-registrations were performed. Slow and fast learning rats did not differ in baseline sleep, but alterations in sleep characteristics were found in relation to learning; after learning, but not after reaching criterium, increases in REM-duration, in number of REM-sleep moments and in spindle activity could be observed, while a decrease in the number of SWS-episodes was found.

The results suggest that sleep during the active phase of the rat, comparable to human naps, may be critically important for the acquisition of a simple operant response; the basis of reward-directed action-outcome learning.

KEY WORDS

Sleep, cognition, instrumental learning, EEG, spindles

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TITLE**THE RELATIONSHIP BETWEEN GENOTYPE AND PHENOTYPE IN VANISHING WHITE MATTER: THE INFLUENCE OF THE SECOND MUTATION****AUTHORS**

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ABSTRACT**Background**

Leukoencephalopathy with Vanishing white matter (VWM) is a rare inherited human neurodegenerative disorder characterized by progressive ataxia and spasticity. Most patients have a childhood onset. VWM is caused by mutations in the genes encoding the subunits of *eukaryotic* initiation factor 2B (eIF2B), a protein complex which has a regulating role in translation. There is an evident variability in the clinical severity and time course of VWM in patients. The underlying explanation for this variability is unknown.

Research question

The R113H mutation in *EIF2B5* is the most frequent mutation in VWM. It is associated with a mild clinical picture, often with adult onset. Because it is so frequent, we have a relatively high number of patients with this mutation in the homozygous or compound heterozygous state. We used data on these patients to answer the question what the influence of the second mutation might be. In some disorders the phenotype is determined by the mildest mutation; in other disorders there is an influence of both mutations.

Results

Of the 172 patients in our database 57 had the R113H mutation in *EIF2B5*. Of the 34 reviewed patients with the R113H mutation, 10 (29%) were homozygous and 24 (71%) compound-heterozygous. The mean age of the 21 living patients was 14.9 years (3.5-60.0); if homozygous 30.1 (10.1-60.0), if heterozygous 8.5 (3.5-28.2). The average onset of the disease was 10 years (2-54); if homozygous 20 (3-54), if heterozygous 6 (2-36). The average age of loss of independent walking was 8 years (2-36); if homozygous at 12 (5-35), if heterozygous at 6 (2-36). Thirteen patients had died (3-39 years); 1 was homozygous (36 years); 12 were heterozygous (3-39).

Conclusion

The clinical variability of VWM patients with a R113H mutation in *EIF2B5* is wide. The homozygous patients have a milder disease course than the compound heterozygous patients. Our data indicate that the phenotype is not determined by the mildest mutation but either by the most severe mutation or by the combination of both mutations.

KEY WORDS

Vanishing white matter, R113H, genotype phenotype correlation

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TITLE
CORRELATIONS BETWEEN OPERANT LEARNING PERFORMANCE AND QUANTITATIVE TRAIT LOCI IN RECOMBINANT INBRED MICE

AUTHOR(S)

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ABSTRACT

Relatively little is known about the functions of 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 learning and memory processes. In this study, we map quantitative trait loci (QTL's) that correlate with behavioural-cognitive abnormalities and particularly in learning and memory. To find QTL's, a large number of C57Bl/6J x DBA/2J (BxD) recombinant inbred mouse lines are screened using appetitive conditioning paradigms.

Food-restricted mice were trained in semi-automated Skinner boxes to press a lever to receive a reinforcer (sucrose pellet). So far, 31 BxD mouse lines and 2 progenitor lines have been screened and analysed (N=5-14 per line). Performance in the last (fifth) session of the operant task (defined as correct trials relative to total number of trials) varied from 7% to 98%. The heritability estimate for the operant performance in the last session of operant conditioning was 17,7% ($p < 0,01$).

QTL mapping was carried out by WebQTL tool. QTL's relevant to the task were found in chromosomes 2 and 9, referring to a mouse gene coding Kcnj3 potassium inwardly-rectifying channel and predicted mouse gene ENSMUSG00000074273, respectively.

KEY WORDS

Mouse behaviour, operant learning, appetitive conditioning, quantitative genetics, behavioural screening, genotype-phenotype interactions, quantitative trait loci, recombinant inbred mice

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TITLE**COORDINATED EVALUATION OF GLIOSIS AND PROLIFERATION IN THE ALZHEIMER HIPPOCAMPUS THROUGH IMMUNOHISTOCHEMISTRY****AUTHORS**

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ABSTRACT

Gliosis and proliferative markers have been previously identified in the hippocampus of pre-senile AD patients¹. Activated astrocytes, expressing glial fibrillary acidic protein (GFAP), increase with oxidative stress and aging in humans and rodents². Additionally, astrocytes can actively degrade A β plaques³ and have been found to increase with A β plaque pathology^{4,5}. Proliferating cell nuclear antigen (PCNA) is known to label glia cell profiles of the brain, however expression of this S-phase marker is poorly understood and may represent mature cell replication, precursor responses, or reactivation of cell cycle during apoptosis. Through double and triple immunohistochemistry (IHC) the relationships between activated astrocytes, PCNA expression, and A β plaque pathology can be carefully evaluated. Preliminary results demonstrate that GFAP expressing cells in the hippocampus do not co-localize with PCNA indicating that activated astrocytes are not replicating in the presence or absence of peripheral A β plaques. PCNA expression was most frequently observed in dementia cases with low Alzheimer pathology and may represent a sensitive measurement of proliferation and apoptosis during advancing stages of disease. This evidence, when evaluated with other protein markers, addresses early pathogenic mechanisms occurring in Alzheimer disease.

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KEY WORDS

Alzheimer disease, gliosis, proliferation, immunohistochemistry, cell cycle

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TITLE
THE NEUROANATOMY OF SEMANTIC VERBAL FLUENCY DEFICITS: IMPLICATIONS FOR PREDICTION

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ABSTRACT

MRI studies of semantic Verbal Fluency (VF) deficits in recent onset schizophrenia report reduced Gray Matter (GM) density in task-related frontal and temporal regions.

This study investigated whether these findings are already present in a clinical population of patients in the putatively prodromal stage of psychosis, in an effort to test whether these task-related GM abnormalities provide a potential trait marker for schizophrenia. The second aim of this study was to examine whether the presence of these abnormalities has predictive power to further identify those patients that will make the transition to psychosis.

Participants were 37 patients at Ultra High Risk for psychosis (UHR Group) of which 10 developed psychosis within 18 months follow-up (Transition Group). Assessment of semantic VF and structural MRI imaging was performed at baseline. Voxel based morphometry was applied to all images using SPM5. The mean GM level was evaluated along with relative score differences on semantic VF tests in 1) the UHR group as a whole, and 2) the Transition Group compared to the non-transitioners (Non Transition Group).

In the total UHR Group, correlational analysis failed to show significant regions of reduced GM density in relation to semantic VF deficits. However, if the Transition Group was compared to the Non Transition Group, deficits in semantic VF were found to be related to impaired GM density the task-relevant regions of the right Medial Temporal Lobe (MTL) and bilaterally in the Anterior Cingulate Cortex (ACC).

These results suggest that reduced GM density known to be associated with semantic VF deficits in schizophrenia is a potential trait marker of the disease and could be a promising finding in identifying more accurately those UHR patients that will make the transition to psychosis.

KEY WORDS

Verbal Fluency, MRI, schizophrenia, Ultra High Risk

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TITLE**SEVERE MULTIPLE SCLEROSIS IS ASSOCIATED WITH LOW STRESS-AXIS ACTIVITY****AUTHORS**

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ABSTRACT**Background and goals**

Stressful life events are known to increase the risk of multiple sclerosis (MS) exacerbations. This phenomenon is thought to be due to inadequate levels of the anti-inflammatory stress hormone cortisol, resulting from strong negative feedback of elevated cortisol levels during stressful episodes. Cortisol is the end product of the hypothalamus-pituitary-adrenal (HPA)-axis, also known as the stress-axis, and is routinely used in its synthetic form, prednisone, to treat relapses of MS. Post mortem and in vivo studies clearly show that the stress-axis is chronically activated in MS. However, in a post-mortem study of 16 MS brain donors, we recently found a highly significant inverse relationship between the responsivity of the stress-axis and severity of MS (Huitinga et al., Ann. Neurol. 2004). Therefore, we performed a follow-up study of 31 female MS brain donors to more specifically determine the consequences of stress-axis activity for severity of MS.

Methods and results

Various clinical, endocrine and neuropathological data of all 31 MS brain donors were analyzed using statistical software. Stress-axis activity was determined by measurement of cortisol levels in corticospinal fluid (CSF). These data clearly confirmed the inverse relationship of stress-axis activity and severity of MS. Moreover CSF levels of tau and glutamate, both indicators of neurodegeneration, correlated with the amount of corticotropin releasing hormone (CRH), which drives the stress-axis. Analysis of the neuropathological reports revealed that donors with low cortisol and severe MS have high numbers of inflammatory demyelinating macrophages, in many cases containing PLP, and no signs of remyelination. Conversely, donors with high cortisol levels and a mild disease course have less activated macrophages and a significantly higher incidence of remyelination.

Conclusions

Our results emphasize the importance of high cortisol levels in overcoming MS inflammation. The observed correlation of both tau and glutamate CSF levels with CRH suggests that neurodegeneration contributes to chronic activation of the stress-axis in MS. Based on these data, we postulate that low stress-axis responsivity leads to more severe MS. Currently, we are performing studies in MS lesions obtained from the Netherlands Brain Bank, to identify glucocorticoid driven mechanisms affecting the pathogenesis of MS lesions, using immunohistochemistry and laser dissection microscopy in combination with Q-PCR analysis (Koning et al., Ann. Neurol. 2007).

KEY WORDS

Multiple sclerosis, stress-axis activity, post-mortem human brain tissue and corticospinal fluid, Q-PCR analysis

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TITLE**CALCIUM TRANSIENTS IN PFC AXONS MEDIATED BY NICOTINIC ACTIVATION: EFFECTS OF AXONAL TYPE III NRG1 SIGNALING****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 gating deficits and impaired performance in short term memory tasks. In addition, nicotinic-mediated glutamatergic transmission is altered at synapses of ventral hippocampal projections (+/-) to nucleus accumbens (nAcc) (+/+). Neurons in the prefrontal cortex (PFC), an area critical for working memory that is also known to project to the nAcc, express Type III Nrg1.

We hypothesize that prefrontal cortical circuits are impaired in Type III 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 physiological effect of Nrg1 deficits in PFC-nAcc circuits are examined in chimeric cocultures of either Nrg1 (+/+) or (+/-) PFC "micro-slices" and WT nAcc neurons. We assess the distribution of nAChRs clusters along axonal projections by focal application of nicotine and quantitative Ca^{2+} -imaging.

Brief application of nicotine increases $[Ca^{2+}]_i$ in PFC axons at multiple "hotspots" along individual axons. Continuous monitoring of WT microslice explants reveals that local fluctuations in Ca^{2+} signals persist for more than 20 minutes. In contrast nicotine induced Ca^{2+} signals in Type III Nrg1 (+/-) PFC axons differs in magnitude, frequencies of fluctuations and duration of the response. Ongoing studies provide a pharmacological and genetic dissection of nAChRs subtypes and their relative contribution to axonal 'hotspots'. In addition, we are assessing the effects of up and down regulation of the levels of Nrg1 by assay of nicotine induced Ca^{2+} signaling in PFC slices with viral mediated expression of Type III Nrg1 constructs.

Current findings support the proposal that Nrg1 expression in presynaptic PFC inputs changes the presynaptic profile of nAChRs and thereby alters the temporal profile of calcium responses to nicotine.

KEY WORDS

nAChRs, neuregulin, prefrontal cortex, nucleus accumbens, calcium

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TITLE**NEW CONCEPTS IN G-PROTEIN COUPLED RECEPTOR SIGNALLING IN THE MESOLIMBIC DOPAMINE SYSTEM****AUTHORS**

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ABSTRACT

The mesolimbic dopamine system is involved in reward signalling, addiction and obesity. Key players in this system are the dopaminergic neurons in the ventral tegmental area (VTA). Activity in this system is largely driven by excitatory and inhibitory synaptic inputs to neurons in the VTA. Importantly, the strength of these inputs is modulated by G-protein coupled receptors (GPCRs). *In vitro* data have revealed two relatively unexplored concepts of GPCR signalling: (1) Constitutive receptor activity; and (2) GPCR (hetero)oligomerization. Our overall aim is to demonstrate the relevance of these two concepts in the mesolimbic dopamine system, by combining pharmacological and electrophysiological strategies. In the current study we focus on the melanocortin 4 receptor (MC4R), which plays a role in dopamine signalling and addiction through an unknown neural mechanism. We use whole-cell patch clamping in murine brain slices to determine how MC4R ligands modulate neuronal input and output in the VTA. Initial results indicate a heterogeneous effect of MC4R agonist NDP-MSH on GABAergic inputs to neurons in the VTA.

KEY WORDS

Ventral tegmental area, melanocortins, constitutive activity, receptor oligomerization

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TITLE**tRNA SPLICING ENDONUCLEASE MUTATIONS CAUSE PONTOCEREBELLAR HYPOPLASIE****AUTHORS**

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ABSTRACT

Pontocerebellar hypoplasias (PCH) represent a group of neurodegenerative autosomal recessive disorders with prenatal onset. Children suffer from severe mental and motor impairments due to atrophy or hypoplasia of the cerebellum, hypoplasia of the ventral pons, microcephaly and variable neocortical atrophy. The disease is progressive and usually patients die before they reach adulthood. We identified a family of PCH type 2 patients in Volendam. Affymetrix 10k SNP arrays and short tandem repeats have been used to identify the PCH2 locus. Sequence analysis of candidate genes in the 2.7 Mb region identified a missense mutation in TSEN54 (A307S) responsible for PCH2 in the Volendam community. We identified the same mutation in 37 of the 42 other PCH2 patients from Europe and Israel.

TSEN54 is one of the four subunits of the tRNA splicing endonuclease (TSEN34, TSEN2 and TSEN15), which is responsible for splicing introns out of tRNA. In our five remaining PCH2 patients we identified in two of them, two missense mutations in TSEN34 (R58W) and in TSEN2 (Y309C). In three cases we could not find a mutation in any of the subunits. Two of our three PCH4 patients were heterozygous for the Ala307Ser mutation, in addition to a stopcodon on the other allele. The third patient carried an additional mutation (S93P) on one of the A307S alleles. The additional mutations in our PCH4 cases suggest a genotype-phenotype correlation, since PCH4 has a more severe course.

KEY WORDS

Pontocerebellar hypoplasia, neurogenetics, tRNA splicing, tRNA splicing endonuclease

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TITLE

ER STRESS IS ASSOCIATED WITH PHOSPHORYLATION OF TAU IN THE PATHOLOGY OF ALZHEIMER'S DISEASE AND PICK'S DISEASE

AUTHORS

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ABSTRACT

Background

The unfolded protein response (UPR) is a protein quality control mechanism that protects cells against endoplasmic reticulum (ER) stress. Previous studies in our group and others have demonstrated involvement of the UPR in Alzheimer's disease (AD). Activation of the UPR is observed relatively early in the disease process in neurons that contain little to no tau pathology^{1,2}, suggesting ER stress precedes tangle formation. In this study we demonstrate activation of the UPR in another tauopathy, Pick's disease (PiD). In addition, we investigate the functional relationship between UPR activation, tau phosphorylation and cell death in a neuroblastoma cell model.

Methods

Immunohistochemistry was used to assay the accumulation of tau and the activation of the UPR in post-mortem brain tissue derived from patients with AD and sporadic Pick's disease (PiD). Specific antibodies for phosphorylated tau, tau isoforms and UPR proteins were used on hippocampus, frontal cortex and temporal cortex from AD, PiD and nondemented control cases. ER stress was induced in a neuroblastoma cell model (SK-N-SH) using tunicamycin and the tau phosphorylation status was assessed using specific antibodies. The role of tau kinases and phosphatases was investigated using selective inhibitors.

Results

Our data indicate a connection between activation of the UPR and phosphorylation of tau. Activation of UPR markers (e.g. BiP, pPERK and pIRE1 α) was observed in AD and PiD neurons that contain little to no tau pathology. Preliminary data indicate that the activity of one of the major tau kinases, glycogen synthase kinase 3 beta (GSK3 β), is increased upon ER stress.

Conclusion

Our data suggest a causal connection between activation of the UPR and tau phosphorylation in both AD and PiD. These observations suggest UPR activation might be an important mechanism in the development of tauopathies. In the future, we wish to further study the relation between UPR activation and tau phosphorylation *in vitro*.

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KEY WORDS

Alzheimer's disease, Pick's disease, ER stress, GSK3 β

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TITLE**THE PHYSIOLOGICAL ROLE OF MEMBRANE MRS IN HIPPOCAMPAL FUNCTION****AUTHORS**

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ABSTRACT

Following stress exposure, the rodent brain is exposed to elevated levels of corticosterone, catecholamines like noradrenaline and neuropeptides. Up till now it was generally thought that noradrenaline and peptides are the main actors in the initial phase of the stress response. Corticosteroids were thought to be important later on, for normalization of brain activity and consolidation of the event, via a genomic pathway. Very recent data from our group, however, show that corticosteroids can also exert rapid non-genomic effects on hippocampal cell properties, via mineralocorticoid receptors in the membrane.

To study the corticosteroid effects on hippocampal functioning of mice, my first goal is to compare CA1 and DG. From preliminary results, differences in the effect of corticosterone on CA1 and DG were observed. In CA1, e.g. an increase in Ca^{2+} currents and mEPSCs amplitude had been seen via delayed genomic pathway and an increase in mEPSCs frequency was observed via rapid non-genomic pathway. In the DG, there was no delayed effect on Ca^{2+} currents. Rapid or delayed effects on mEPSCs were not examined yet. We hypothesize that corticosterone 1) rapidly changes the mEPSC frequency but 2) that there is no delayed effect on mEPSCs in DG. Preliminary observations indeed support the former; I am presently examining the latter hypothesis.

Also, in this project I want to investigate the physiological importance of the rapid corticosteroid effects by studying variations in CA1 and DG mEPSC properties during pulsatile corticosterone release. We propose that the membrane mineralocorticoid receptors are the only means for hippocampal cells to *quickly and accurately* translate fluctuations in hormone level into changes in electrical activity.

KEY WORDS

Corticosterone, hippocampus, CA1, Dentate Gyrus, mEPSCs, delayed genomic pathway, rapid non-genomic pathway, MRs

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TITLE**THE CORTISOL AWAKENING RESPONSE IN DISRUPTIVE BEHAVIOUR DISORDERS COMPARED TO NORMAL CHILDREN****AUTHORS**

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ABSTRACT

Disruptive Behaviour Disorders (DBD) incorporates both Oppositional Defiant Disorder and the more severe Conduct Disorder. Both include children or adolescents who are hostile, aggressive and display antisocial and delinquent behavior. This behavior could be explained by means of decreased levels of neurobiological arousal, constituting a aversive physiological state. In order to increase this neurobiological activity, these children seek stimulation, often through antisocial behavior. Another theory states that these children are fearless, they do not physically feel fear in situations where most people would.

One of the neurobiological systems involved in regulating stress and arousal is the Hypothalamic-Pituitary-Adrenal (HPA)-axis. Many studies confirm that cortisol, the main stress hormone produced by the HPA-axis, is indeed decreased in children with DBD (Raine 1997; van Goozen 1998; McBurnett 2000; Popma et al 2006).

However, to determine whether decreased cortisol levels precede DBD, and are also associated with related behaviors, a prospective study in a non-clinical population is required. This study will therefore investigate the relation between 1) cortisol and DBD, and 2) cortisol and behaviors associated with DBD, such as aggression and delinquency.

For this study 343 13-year old boys and girls, of which half at high risk of developing DBD, were selected. Cortisol was measured in saliva, collected immediately after awakening, 30 and 60 minutes later, of which a Cortisol Awakening Response (CAR) could be derived. A DBD diagnosis was established by means of the DISC (Diagnostic Interview Schedule for Children), and dimensional measures of DBD related behaviors (e.g. Child Behavior Checklist) were also collected. Preliminary data will be presented.

KEY WORDS

Disruptive behavior disorders, aggression, delinquency, cortisol, HPA-axis

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TITLE**AVALANCHE DYNAMICS OF ONGOING OSCILLATIONS *IN VITRO*, *IN VIVO*, AND IN COMPUTATIONAL MODELS****AUTHORS**

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ABSTRACT

Human brain oscillations fluctuate erratically in amplitude during rest and exhibit a power-law decay of temporal correlations on long time scales (1). It has been suggested that these dynamics reflect self-organized activity near a critical state. In this framework, oscillation bursts may be interpreted as neuronal avalanches propagating in a network with a critical branching ratio (2). However, a direct comparison of the temporal structure of ongoing oscillations *in vivo* with that of activity propagation in a model network with critical connectivity and the oscillation burst structure *in vitro* has never been made.

Here, we simulate branching processes and characterize the activity propagation in terms of avalanche life-time distributions and temporal correlations. We introduce an equivalent analysis for characterizing ongoing oscillations *in vitro* and *in vivo*. We found that models in the critical state exhibited power-law scaling in avalanche life-time distributions with similar scaling exponents as observed for carbachol induced oscillations in mouse hippocampal slices and as resting-state alpha oscillations in humans (magnetoencephalography). The model and *in vitro* data reproduced qualitatively the power-law decay of temporal correlations seen *in vivo*; however, the correlations only appeared on time scales up to the longest burst event, whereas *in vivo* oscillations indicate persistence of correlations on time scales corresponding to several burst events. Our results support the idea that neuronal networks generating ongoing alpha oscillations during rest operate near a critical state, but also suggest that factors not present in the simple branching-process model or *in vitro* (e.g., modulation by sub-cortical structures) are needed to account for the complex temporal structure of *in vivo* oscillations on time scales longer than the duration of individual oscillatory bursts.

References

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KEY WORDS: Oscillations bursts, avalanches, ongoing oscillations, resting-state, branching processes, power-law scaling, magnetoencephalography (MEG), neuronal networks, hippocampal oscillations

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TITLE
THE ROLE OF ATTENTION IN FIGURE-GROUND SEGREGATION

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ABSTRACT

The segregation of a visual scene into figure and ground is a fundamental problem to be solved by the visual system. Even with the same classical receptive field (cRF) stimulation, neurons in primary visual cortex (V1) have an enhanced response when their cRF is on a figure compared to when it is on the background, an effect known as Figure-Ground Modulation (FGM).

We investigated the effect of attention on FGM by presenting monkeys with the same stimulus but requiring them to perform two different tasks: one in which they had to make saccades to the figure, and one in which the figure and ground were irrelevant and a different attention demanding task had to be performed. We recorded Multi-Unit Activity (MUA) simultaneously from area V1 and area V4.

We present data that shows that at some of the recording sites, attention affects figure ground modulation. Whereas FGM remains present when the RF is on the edge, when the figure is not relevant, it disappears when the RF is in the centre of the figure. This suggests that for these sites, attention is necessary for perceptual filling in.

KEY WORDS

Visual cortex, attention, figure-ground

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TITLE
MODULATION OF SYNAPTIC INPUTS TO LAYER II/III PYRAMIDAL NEURONS IN THE PREFRONTAL CORTEX BY NICOTINE

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ABSTRACT

The prefrontal cortex (PFC) is critically involved in cognitive functions such as selective attention behavior. Nicotine improves attentional performance in rodents and humans, and nicotinic receptors are abundantly expressed in the PFC. In addition, nicotinic receptor stimulation is beneficial to people suffering from impaired attention performance, in diseases such as Alzheimer and Schizophrenia. Understanding how activation of these receptors by nicotine influences prefrontal cortex functioning will be crucial for developing drug targets to alleviate attentional deficits. We are only beginning to understand how nicotine influences prefrontal cortex microcircuit functioning. In PFC layer V, nicotine excites different types of interneurons through activation of multiple nicotinic receptors. By increasing GABAergic inhibition onto pyramidal neurons, nicotine increases the threshold for spike-timing dependent potentiation of glutamatergic synapses. Whether this holds true for layer II/III as well is not known. Therefore, we addressed the question of how nicotine influences synaptic communication in PFC layer II/III. We found that bath application of nicotine increases GABAergic currents onto pyramidal cells, while the glutamatergic inputs are unaffected. Currently, we investigate which nicotinic receptors are involved in enhancing inhibition and on what type of interneurons they are located.

KEY WORDS.

Nicotine, prefrontal cortex, microcircuits, inhibition, interneurons

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TITLE**TRIPLE REUPTAKE INHIBITORS: BEHAVIORAL AND MICRODIALYSIS STUDIES IN THE OLFACTORY BULBECTOMY MODEL OF DEPRESSION****AUTHORS**

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ABSTRACT

The currently available antidepressants, SSRIs, are relatively safe to use, but induce adverse side effects, such as sexual dysfunction, as long as the patients take their medication.

New promising drugs are the triple reuptake inhibitors (TRIs), which not only work on serotonin (5-HT) and norepinephrine (NE), but more important, also increase dopamine (DA) transmission. By working on dopamine, the TRIs are believed to play an important role in the treatment of anhedonia (loss of pleasure), one of the core symptoms of depression.

We used the removal of the olfactory bulbs (OBX) in Sprague Dawley rats as an animal model of depression. OBX results in altered neuroendocrinology and behavior in animals, which can be normalized by chronic, but not acute treatment with antidepressants. We tested the chronic and acute actions of the triple reuptake inhibitor DOV216,303 in OBX and sham operated rats and performed behavioral studies and microdialysis studies to measure the monoamine release in the prefrontal cortex.

Our microdialysis study showed that after acute injection of DOV216,303 (20 mg/kg i.p.) all monoamine levels were increased. But after chronic treatment with DOV216,303 only 5-HT baseline levels were significantly increased. In our behavioral study, treatment with DOV216,303 has antidepressant behavioral effects in the open field paradigm, but no sexual side effects were observed.

KEY WORDS

Triple reuptake inhibitors, microdialysis, OBX, depression, anhedonia

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TITLE**ANTI-EPILEPTIC DRUG INTERACTIONS WITH α -SUBUNITS OF VOLTAGE-GATED Na^+ CHANNELS STABLY EXPRESSED IN HEK293 CELLS****AUTHORS**

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ABSTRACT

Voltage-gated Na^+ channels play an important role in the generation and propagation of action potentials in excitable cells like neurons. Na^+ channels are composed of a pore-forming α -subunit and auxiliary β -subunits, and four different types of α -subunits ($\text{Na}_v1.1$, $\text{Na}_v1.2$, $\text{Na}_v1.3$ and $\text{Na}_v1.6$) comprise the human brain Na^+ channels. Several anti-epileptic drugs (AEDs) such as carbamazepine (CBZ), phenytoin (DPH), lamotrigine (LTG) block Na^+ channels in a use-dependent manner. Pharmacoresistance is a common phenomenon in epilepsy patients where during time AEDs can lose their therapeutic efficacy. The target hypothesis suggests that the targets of AEDs, e.g. Na^+ channels, may undergo pharmacological and functional modifications, and can thus be a mechanism underlying pharmacoresistance. Indeed, in epileptic brain tissues, Na^+ channels have been shown to be modified in both physiological function and subunit expression pattern. The $\text{Na}_v1.3$ subunit, which is mainly expressed in embryonic and neonatal brain, is found to have an increased expression pattern in brain tissue of epilepsy patients and animal models for epilepsy. To explore whether this expression pattern change plays a role in pharmacoresistance, we compare the interaction of AEDs with different Na channel α -subunits.

We use HEK293 cell lines which stably express the four human α -subunits as preparation and the whole-cell voltage clamp technique to record Na^+ currents carried by these α -subunits. We investigate the pharmacological properties of three AEDs (CBZ, DPH and LTG), where we determine AED effects on steady-state inactivation, removal of inactivation and the binding and unbinding rates of the AEDs to the α -subunits. Pilot data show that the AEDs have slower binding rates to the $\text{Na}_v1.3$ subunit than to the other three α -subunits. The conclusion so far is that the slower binding rates of AEDs to $\text{Na}_v1.3$ α -subunits might partly explain the reduced sensitivity to AEDs and consequently pharmacoresistance in some epilepsy patients.

KEY WORDS

Epilepsy, pharmacoresistance, Na^+ channel

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TITLE
QUANTITATIVE PROTEOMICS OF MEMORY CONSOLIDATION IN TWO INBRED MOUSE STRAINS

AUTHORS

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ABSTRACT

The molecular key players in the processes of memory consolidation and memory retrieval are largely unknown. The two mouse inbred strains C57BL/6J and DBA2/J display differences in hippocampus-dependent learning. The main aim of this project is to assess the type and time-course of protein expression that is actively involved in memory consolidation and (re-)consolidation using a dorsal hippocampus-dependent learning task, i.e. contextual fear conditioning in these two strains.

In this study we have first assessed the difference in memory retention by measuring freezing behavior at different time points after training in mice from both strains in contextual fear conditioning. In order to understand the molecular mechanisms, occurring both during and as a consequence of fear memory observed during the retention test, a proteomics approach (C57 strain) was used to identify and quantify proteins in synapses of the dorsal hippocampus. Synaptic protein expression analysis 1 and 4 h after the memory retention test performed 24 h after training showed temporal down-regulation of glutamate receptor (AMPA) subunits and AMPAR-interactors at the synapse. The down-regulation of these identified proteins was confirmed by Western blot analysis. These memory reactivation-induced differences may be attributed to stimulated trafficking of AMPARs at the activated post-synapse, which would in turn rapidly regulate synaptic strength.

To test the hypothesis that cycling AMPARs play an integral role in the process of memory (re-)consolidation, we will inhibit regulated AMPAR endocytosis *in vivo* by use of a synthetic peptide derived from the GluR2 carboxyl tail.

KEY WORDS

Inbred mice, memory consolidation, fear conditioning, AMPA receptor, hippocampus

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TITLE**COGNITIVE DECLINE IN TYPE 2 DIABETES MELLITUS: A LONGITUDINAL POPULATION-BASED STUDY****AUTHORS**

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ABSTRACT

Background Type 2 diabetes (DM2) is associated with an increased risk of cognitive dysfunction. In a previous study we have shown that patients with an average DM2 duration of 8 years perform worse than controls on the domains memory, information processing speed and attention and executive functioning (mean difference in z-scores 0.2 – 0.4). Patients and controls were reexamined after a 4-year interval.

Methods The abstract contains data from an interim analysis of 41 DM2 and 26 control participants. Follow-up of the whole population will be completed by December 2008. Test scores were divided into five cognitive domains (memory, attention and executive functioning, speed of information processing, abstract reasoning and visuoconstruction) and expressed as standardized z-values, adjusted for age, sex and level of education. The follow-up and baseline data were analysed with an ANOVA for repeated measurements.

Results Cognitive domain z-scores were lower in the DM2 group (mean differences: memory 0.13, attention and executive functioning 0.11 and information processing speed 0.30), but with the current sample size the overall effect of group was not statistically significant. There was no significant effect of time or interaction between group and time on any of the cognitive domains.

Conclusion In this small sample of non-demented individuals with DM2 we find modest, non significant decrements of cognitive functioning, with effect sizes that are compatible with previous studies. We could not demonstrate accelerated decline in the DM2 group. Apparently, cognitive decrements in DM2 develop very slowly, over a much longer time frame than the 4 years sampled in the current study.

KEY WORDS: Type 2 diabetes, cognitive performance, neuropsychological investigation

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TITLE

***MLC1* MUTATIONS CAUSE DYSFUNCTION OF CHLORIDE CHANNEL ACTIVITY, A DISTURBANCE OF VOLUME REGULATION, AND CEREBRAL WHITE MATTER EDEMA**

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 plasma – membrane protein of unknown function which is expressed in leukocytes and in astrocytic endfeet at the blood-brain and cerebrospinal fluid-brain barriers. We tested the hypothesis that MLC1 is associated with ion channel function. Whole-cell voltage-clamp experiments were performed on *Spodoptera frugiperda* (Sf9) insect cells transfected with either wild-type or mutant MLC1 constructs, before and after cell volume changes were induced by a hypotonic challenge. This study demonstrated that MLC1, a protein mainly located in astrocytic endfeet in the brain is involved in chloride transport associated with volume regulation. The findings that MLC1 expression in Sf9's insect cells, which do not contain a MLC1 orthologue, induces a chloride current profile, strongly suggest that the MLC1 protein itself harbors a channel function. Our findings imply that a defect in chloride channel activity in astrocytes affecting volume regulation underlies the white matter edema in MLC patients.

KEY WORDS

MLC1, astrocytes, Sf9's, electrophysiology, chloride channel, volume regulation, leukodystrophy

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TITLE**MYOCLONUS-DYSTONIA: CLINICAL AND GENETIC EVALUATION OF A LARGE COHORT****AUTHORS**

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ABSTRACT**Background**

Myoclonus-Dystonia (M-D) is an autosomal dominantly inherited movement disorder. Various mutations within the *epsilon-sarcoglycan* (*SGCE*) gene have been associated with M-D, but mutations are detected in only about 30% of patients. The lack of stringent clinical inclusion criteria and limitations of mutation screens by direct sequencing might explain this observation.

Methods

Eighty-six M-D index patients from the Dutch national referral center for M-D underwent neurological examination and were classified according to previously published criteria into definite, probable and possible M-D. Sequence analysis of the *SGCE* gene and screening for copy number variations were performed. In addition, we screened for the 3-bp deletion in exon 5 of the *DYT1* gene.

Results

Based on clinical examination, 24 definite, 23 probable and 39 possible M-D patients were detected. Thirteen of the 86 M-D index patients carried a *SGCE* mutation: seven nonsense mutations, two splice site mutations, three missense mutations (two within one patient) and one multi-exonic deletion. In the definite M-D group 50% carried a mutation. In the probable group only one single patient carried a *SGCE* mutation (3%). One possible M-D patient showed a 4-bp deletion in the *DYT1* gene (c.934_937delAGAG).

Conclusions

Mutation carriers were mainly identified in the definite M-D group. However, in half of definite M-D cases no mutation could be identified. Copy number variations did not play a major role in our large cohort.

KEY WORDS

Myoclonus dystonia, phenotype, genotype, DYT11

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TITLE**REPLICATION OF CANDIDATE GENES, LOCUS-WIDE ASSOCIATION STUDY FOR IQ****AUTHORS**

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ABSTRACT

One of the major hurdles in identifying genes for complex traits is the lack of replication to distinguish false positives from genuine associations. Of all reported genetic association studies, only 4% have shown replicable findings. The recent growth in large (publicly available) datasets that contain both whole genome association data as well as a wealth of phenotypic data, serves as an excellent resource for rapid replication efforts. We used the publicly available data of 947 families participating in the International Multi-centre ADHD Genetics (IMAGE) consortium to attempt replication of previously reported candidate genes for intelligence, and to conduct a finemapping study of previously associated genomic locations. We tested 688 single nucleotide polymorphisms (SNPs) within 16 previously reported candidate genes (DNAJC13, TBC1D7, FADS3, BDNF, APOE, PRNP, CBS, DRD2, IGF2R, CHRM2, CTSD, SNAP25, COMT, KLOTHO, ALDH5A1 and DTNBP1) and 5922 SNPs in 6 genomic locations (2q24.1-31.1, 2q31.3, 6p25-21.2, 7q32.1, 14q11.2-12 and 16p13.3) previously identified through whole genome linkage and association analyses.

Thirteen of the sixteen candidate genes showed SNPs with P-values below .05, with the most significant SNPs in the COMT gene (rs737865; P-value= 4.8×10^{-5}), and the DTNBP1 gene (rs875463; P-value= 4.0×10^{-4}). In the genomic areas, four new candidate genes for intelligence were identified: ATF2, FAM65B, IER3 and CPNE5 (P-value $\leq 5 \times 10^{-6}$). These new genes are involved in neuronal development, cell differentiation and proliferation.

KEY WORDS:

Intelligence, replication, association

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TITLE**THE APPLICABILITY OF BIOLUMINESCENCE TO MEASURE CELL SURVIVAL AFTER IMPLANTATION IN RAT SPINAL CORD****AUTHORS**

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ABSTRACT

The implantation of specific cell types is a promising therapeutic strategy for the treatment of spinal cord injuries. Unfortunately, the environment in the damaged spinal cord is hostile for implanted cells leading to necrosis of most implanted cells. Bioluminescence is a non-intrusive technique that might be utilized for in vivo monitoring of the survival of implanted cells in rats. To validate the applicability of luminescence in a pilot study, we transduced adult rat Schwann cells (SC) with a lentiviral construct encoding the luciferase 2+ gene and injected these cells in the spinal cords of Fischer 344 rats. 2 Groups were included; the first group consisted of 2 rats that received a laminectomy at T-8 followed by 3 injections containing 5×10^5 SC's. The second group consisted of 3 rats that were given unilateral rubrospinal tract lesions at thoracic vertebrae 8 (T-8) followed by 3 injections in and around the lesion containing a total of 5×10^5 SC's. The luminescence was measured with an IVIS 100 at 0, 3, 7, 10, 17, 24, 35, 43, 48, 49, 62, 65, 77 days after surgery by injecting 150mg/kg luciferin IP or IV just before each measurement. Subsequently, rats were perfused and cell numbers still present in the spinal cords were determined by IHC. At day 0, the signal was very weak which could most likely be attributed to a wound quenching effect. At day 3 the signal was strong and subsequently it slowly decreased until approximately 10x background at day 24 which is in line with earlier histological observations. From day 24 the luminescent signals reached a plateau phase indicating a stabilized cell number. Compared to IP injections, the luminescence after IV injections has a significantly higher amplitude and less variability. Finally, the average number of photons/s/cell was determined at the last time point. These preliminary data are very promising and we will further investigate the applicability of bioluminescence for spinal cord research.

KEY WORDS

Bioluminescence, spinal cord, regeneration, Schwann cells, longitudinal

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TITLE
SKIN TEMPERATURE AS A PREDICTOR FOR LAPSES IN VIGILANCE

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ABSTRACT

The preoptic area and anterior hypothalamus (POAH) contain neurons that are essentially involved in both sleep- and thermo-regulation. In this area, and several other brain areas involved in sleep regulation, neuronal activity can be modulated by mild warming and cooling of the skin. Previous studies in humans showed that sleep onset latency and performance on a sustained vigilance task are sensitive to mild skin temperature manipulation^{1,2,3}. So far little is known about the predictive properties of unmanipulated skin temperature for lapses in vigilance. We performed a validation of the predictive value of spontaneous fluctuations in skin temperature for the risk of lapses and slow reactions in a sustained vigilance task. Eight healthy participants (5 males, 22-47 years of age) underwent vigilance assessment for two days, in 4 task sessions per day. The four consecutive task sessions started at 09.00 with two hour intervals. During each session, participants were asked to perform a psychomotor vigilance task for 20 minutes while sitting in a dimly lit room. Skin temperature was monitored at several locations throughout the task, whereafter temperature in relation to response speed and lapses were analyzed. Especially proximal skin temperature measured subclavicularly was able to predict lapses in vigilance. These findings are consistent with earlier studies which showed that manipulation of proximal skin temperature is able to influence both sleep onset latency as well as vigilance, thereby strengthening the arguments for the hypothesis that skin temperature is a causal element in the sleep/wake cycle¹.

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KEY WORDS

Skin temperature, vigilance, attention

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TITLE

OLFACTORY ENSHEATHING GLIA AND THE REGENERATION OF THE OLFACTORY SYSTEM: INVOLVEMENT OF PHAGOCYTOSIS, CHOLESTEROL RECYCLING AND MODULATION OF THE EXTRACELLULAR MATRIX

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ABSTRACT

The primary olfactory nervous system regenerates successfully after neuronal damage. Regenerating olfactory axons grow out over long distances and achieve highly accurate targeting inside the central nervous system. Axonal outgrowth from new neurons in the olfactory epithelium (OE) is supported by olfactory ensheathing glia (OEG), which engulf outgrowing axons all along the olfactory nerve and are the main cell type in the olfactory nerve layer (ONL). A preceding study was aimed at revealing the molecular mechanisms involved in axonal outgrowth in the olfactory system after a lesion. In this microarray study the most prominent genes pertained to phagocytosis, cholesterol recycling and extracellular matrix (ECM)-modulating genes which may directly be involved in axonal regeneration. Our aim is firstly, to validate the functional relevance of these genes with an in vitro model for phagocytosis and neurite outgrowth and secondly, by in vivo validation of protein expression. The microarray data indicated the coordinated upregulation of complement factors, Fc receptors and the Vav1-Rac2-Wasp pathway, which may all be part of the phagocytic response. In addition, the cholesterol biosynthetic pathway was simultaneously downregulated, which may be due to the increased uptake of debris-derived cholesterol by phagocytosis. In the phagocytosis assay, purified primary OEG cultures will be exposed to different types of debris and RTqPCR will be performed to quantitatively measure the differential expression of these genes, compared to a basal (control) expression. The involvement of ECM-modulating genes in axonal regeneration will be functionally validated by siRNA-mediated knockdown in a neurite outgrowth assay. Data from this assay may allow us to generate a shortlist of genes that will be tested in an overexpression assay. Finally, the in vivo protein expression of a selection of these different types of genes (phagocytosis, cholesterol biosynthesis and ECM) will be validated by immunohistochemical localization in the ONL after a lesion.

KEY WORDS

OEG, Phagocytosis, Vav1-Rac2-Wasp pathway, cholesterol biosynthesis, extracellular matrix, immunohistochemistry

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TITLE**NORMAL CORTICAL EXCITABILITY YET POLYPHASIC MEP'S IN MYOCLONUS DYSTONIA - A TMS STUDY****AUTHORS**

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ABSTRACT**Objective**

The aim of the present study is to investigate cortical excitability in patients with DYT 11 positive Myoclonus-Dystonia (M-D), using transcranial magnetic stimulation (TMS).

Methods

Silent period, motor evoked potential recruitment curve, short interval intracortical inhibition (SICI), intracortical facilitation (ICF) and short interval intracortical facilitation (SICF), with short interstimulus intervals ranging from 1.2 to 3.2 ms, in 15 DYT11-positive M-D patients and their matched controls were studied.

Results

All TMS parameters were normal compared to healthy controls, except for the SICF protocol, as in M-D more variable and polyphasic MEPs were detected. Cross-covariance analysis of MEP area revealed a significant correlation difference at ISI 2.2, 2.4 and 2.8 ms with a significant time course effect on MEP variability over all ISI ($p < 0.0001$). This increased variability was not seen in the other TMS protocols.

Conclusions

The asynchronicity of MEPs during the SICF protocol in M-D patients is likely to reflect central neuron membrane instability. This abnormality might contribute to impaired control of movement in M-D. Application of the SICF protocol in other patient groups has to prove its value in movement disorders.

KEY WORDS:

Myoclonus dystonia, polyphasic MEP, transcranial magnetic stimulation, I-wave asynchronicity

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TITLE**ENDOCANNABINOID SIGNALLING IN THE PREFRONTAL CORTEX****AUTHORS**

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ABSTRACT

The endocannabinoid (eCB) system plays a major role in maintaining metabolic equilibrium in vertebrates. Biological functions regulated by eCBs include appetite, body temperature, blood pressure, reproductive activity, learning capacity, and motor coordination. In the central nervous system (CNS), eCBs are implicated to modulate the neurotransmission of several classical transmitters such as GABA and glutamate. Studies to the effects of eCBs in the hippocampus have demonstrated that these ligands are primarily involved in the synaptic transmission of inhibitory (GABA) and excitatory (glutamate) transmitters. Moreover, the modulation of neurotransmission showed to be attained through retrograde signaling, which entails that activation of the postsynaptic neuron, instead of the presynaptic cell, triggers the synthesis and release of eCB's. These ligands subsequently bind to the eCB receptors on the presynaptic neuron. The calcium influx into the presynaptic cell is attenuated as a result of binding to the eCB receptors which in turn inhibits the release of neurotransmitters. This manner of inducing short-term synaptic plasticity is therefore characterized as depolarization-induced suppression of inhibition (DSI) and excitation (DSE), respectively and appears to be typical for eCB signaling. It is believed that malfunctioning of the eCB system in the CNS might cause biochemical imbalances in the brain circuitries which can exacerbate or even cause pathological disorders such as addiction, schizophrenia and mood disorders. The aim of this project is to investigate the role of the brain endogenous cannabinoids in addiction and mental disorders. To achieve this we investigate the involvement of the eCBs in the regulation of mesocorticolimbic neurotransmission at the cellular level. We apply the whole patch-clamp technique to investigate the effects of eCBs, CB agonists and antagonists on short term plasticity (DSI/DSE) in the prefrontal cortex, a brain area implicated to be involved in cognition and impulse control. Ultimately the therapeutic opportunities of cannabinoid ligands as treatment for addiction and mental disorders will be explored as well.

KEY WORDS: endocannabinoid system, prefrontal cortex, neuronal signaling, CB1 agonist, CB1 antagonist

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TITLE
VOXEL BASED MORPHOMETRY OF THE TRANSEXUAL ADOLESCENT BRAIN

AUTHORS

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ABSTRACT

Sex differences in cognition, gender identity and sexual orientation may all reflect sex-related neuroanatomical differences in the human brain. Earlier studies have shown sex differences in the amount of gray and white matter and also in the total amount of cerebrospinal fluid. In transsexual people a reversal of the sex difference in the Bed Nucleus of the Stria Terminalis has been observed.

We hypothesize that in transsexualism the brain develops to some extent in the direction of the desired sex and not only in the direction of the biological sex.

The present study focuses on differences between transsexual adolescents and similarly aged individuals of both sexes, by determining the total amount of gray and white matter as well as the total amount of cerebrospinal fluid.

In total 120 Male and female transsexual adolescents of 9-25 years old will be recruited. 12 MF and 12 FM transsexual patients will be included in five groups (1. ca 9-10 years, 2. ca 12 years, 3. 16 years, 4. 17 years and 5. 18-19 years). In addition, control subjects will be recruited: one male and one female friend for each transsexual patient.

Magnetic resonance imaging (MRI) includes a coronal 3D gradient-echo T1-weighted sequence (matrix 256 x 256, voxel size 1 x 1 x 1.5 mm, 170 sections) for structural MRI and will be performed on a Philips Intera 3.0 Tesla with a standard 8-channel head coil.

Voxel-based morphometry will be used to examine the total brain volume and the amounts of gray and white matter and CSF. VBM will be performed using the SPM5 software package. We will present the first data on structural MRI's of about 50 adolescents

KEY WORDS

VBM, adolescents, transsexuality

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TITLE
RANKING YOUR COGNITION

AUTHORS

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ABSTRACT

Background

Insight of possible cognitive decline or disorders is crucial for estimating one's own cognitive functioning.

Methods

The self-evaluation strategies of subjects for competence in cognitive functioning and possible age-related effects were assessed. Young (n=15) and middle-aged (n=15) subjects matched for education, self-estimated competency in reasoning, memory, concentration, visual perception and language, before and after these abilities were measured with standardized neuropsychological tests. The difference between estimated and actual performance, corrected for overall performance, resulted in an Estimation Error (EE); with EE = 0 as perfect estimation, a negative EE (≥ -1) as underestimation and overestimation a positive EE (≤ 1).

Results

The EEs differed between cognitive domains. Subjective adaptation towards an underestimation error is selectively present for memory in both age groups. Pre-test memory overestimation is present in the middle-aged. This might reflect a compensation-bias towards expected memory decline with age.

Discussion

Different EEs between cognitive domains suggest a diversified rather than a unitary notion of cognitive functioning. Therefore, more detailed screening of self-estimation in cognitive functioning yields clinical significance. Overestimation related to age-related expected memory decline appears accessible for correction after confrontation with actual performance. Further research can verify whether post-test correction (for overestimation) happens for other impaired cognitive domains.

KEY WORDS

Cognitive functioning, self-estimation accuracy

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TITLE**INITIAL AGE OF CANNABIS USE AND THE RISK OF PSYCHOTIC SYMPTOMS****AUTHORS**

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ABSTRACT

Cannabis seems to play a causal role in the development of psychotic disorders at population level but it is unknown what the magnitude of this effect is and what characteristics predispose to such an effect. We conducted the single largest population study on the association between cannabis use and psychotic symptoms, focusing on the hypothesis that this association is enhanced in individuals with an early age of first cannabis use. As a measure for psychosis symptoms, we used the Community Assessment of Psychic Experiences (CAPE) that was administered through the internet. We assessed the amount of euros (€) spent on cannabis as a strongly correlated proxy measure of exposure to Δ -9-Tetra-Hydro-Cannabinol (THC) (4). The 13,888 respondents (48% female) had a mean age of 22.4 years. We found that CAPE-scores increased significantly as THC exposure accumulated (F-score: 64.395, df:5, $p < 0.001$). Furthermore, the age at which cannabis use is started had an independent main effect on the occurrence of psychotic symptoms (F-score: 16.0, df: 4, $p < 0.001$). This effect was particularly strong in those starting cannabis use before age 15 ($n=2,134$) and was most prominent for positive symptoms (F-score: 76.624, df: 1, $p < 0.001$). Furthermore, this group used more cannabis and more often had a psychiatric history. Our study corroborates earlier findings in a new, large dataset and suggests that the risk of a psychotic outcome is particularly elevated for those starting cannabis use before age 15. Policymakers need to take measures to inform the general public on the (psychiatric) risks of cannabis use, especially in the young.

KEY WORDS

Cannabis, psychosis, psychotic symptoms, substance abuse

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TITLE**FAST AND SLOW SPINDLES RELATE INVERSELY TO MOTOR SKILLS IN PRIMARY SCHOOL AGED CHILDREN****AUTHORS**

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ABSTRACT

Although convincing evidence exists for the role of sleep in memory consolidation in adults, there remains a scarceness of studies investigating sleep-dependent learning in children. During childhood, learning abilities are especially high and both macroscopic and microscopic aspects of sleep are clearly distinct from adult sleep features.

The current data were obtained during the Great Sleep Experiment, a large-scale project on the relationship between children's sleep and their cognitive performance. These data were acquired in a motor skill learning task: the finger tapping task. Subjects (10.8 + 0.9 years; mean + SD) performed three versions of the task, each containing a different consolidation period: 12 hours containing Wake, 12 hours including Sleep, and 24 hours containing both Wake and Sleep. Throughout the 12-hour Sleep period, polysomnographic recordings were performed. Besides standard visual sleep scoring, automated detection algorithms were used for spindles and slow oscillations.

Interestingly, the behavioural data revealed enormous sleep-dependent improvements, but only for performance accuracy: +49% in the Sleep condition and +47% in the Wake & Sleep condition ($p < 0.001$). Performance speed showed large improvements regardless of condition: +32% in the Wake condition, +45% in the Sleep condition, and +33% in the Wake & Sleep condition. Preliminary results of the spindle analyses revealed that baseline performance levels were positively correlated to the density of fast frontal spindles ($r = 0.52$, $p = 0.01$), and negatively correlated to the density of slow frontal spindles ($r = -0.58$, $p < 0.01$).

In conclusion, children - comparable to adults - show sleep-dependent consolidation of a motor skill, but - unlike adults - they also display enhanced performance over a period of wakefulness. The thalamo-cortical oscillations apparent during preadolescent sleep appear to relate to general motor skill ability, and may provide an indication of neuronal maturation.

KEY WORDS:

Sleep, learning, memory, development

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TITLE**STABLE HISTAMINE PRODUCTION IN SPITE OF EXTENSIVE PARKINSON PATHOLOGY IN THE HYPOTHALAMIC TUBEROMAMILLARY NUCLEUS****AUTHORS**

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ABSTRACT

The hypothalamic Tuberomamillary Nucleus (TMN) is the exclusive source of histamine in the brain. Previous studies have reported conflicting data on the nature and direction of the alterations in the Tuberomamillary Nucleus (TMN) in Parkinson's disease (PD). On one hand it was thought that the extensive presence of Lewy bodies (LBs) and Lewy neuritis (LNs) in the TMN indicated a strong degeneration of the TMN in PD, whereas other data indicated an activation of the TMN that was even presumed to accelerate degeneration of the substantia nigra in the course of PD. We aimed to clarify this controversy by quantitative in situ hybridization for the mRNA of the rate limiting enzyme histidine decarboxylase (HDC) as a marker for histamine production in post mortem human brain tissue from PD patients (early PD stages n=6, late PD stage n=11) and 17 controls that were matched. The brain material was obtained from the Netherlands Brain Bank. Furthermore we determined the relationship between HDC expression in the TMN and the amount of typical PD lesions, i.e. the LBs and LNs in this area. The main result of the present study was that the HDC expression in the TMN was unaltered, both in early and late stages of PD, in spite of the extensive PD lesions in this area.

Acknowledgement

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KEY WORDS

Parkinson, histamine , histidine decarboxylase , lewy bodies

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TITLE**SPECIFIC DEFICITS IN SOCIAL INTERACTION IN MICE LACKING THE 5-HT_{3A} RECEPTOR****AUTHORS**Laura A. Smit-Rigter, J.A. van Hooft**DEPARTMENT/INSTITUTE**

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ABSTRACT

In the brain, the 5-HT_{3A} receptor is mainly expressed on interneurons, but also on Cajal Retzius cells. Recent findings showed that the 5-HT_{3A} receptor expressed on Cajal Retzius cells plays a key role in cortical development by regulating dendritic development. Analysis of the 5-HT_{3A} knock-out mouse showed aberrant growth of the dendritic tree of layer II/III pyramidal neurons in the somatosensory cortex. However, neurological examination did not reveal any abnormalities in this mouse so far, apart from a decrease in anxiety in the 5-HT_{3A} knock-out mouse. Here, we show that the 5-HT_{3A} knock-out mouse displays specific deficits in social interaction which are not due to changes in olfaction and anxiety. These results show that the 5-HT_{3A} knock-out mouse displays a phenotype reminiscent to neurodevelopmental disorders such as autism.

KEY WORDS5-HT_{3A} receptor, cortical development, social behavior**TELEPHONE-NUMBER:** 020-5257705**E-MAIL-ADDRESS:** l.rigter@uva.nl

TITLE
FEMALE SEXUAL BEHAVIOR AND PHARMACOLOGY IN SEROTONIN TRANSPORTER (SERT) KNOCKOUT RATS.

AUTHORS

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ABSTRACT

Sexual dysfunctions are the main side effects of selective serotonin reuptake inhibitors (SSRIs). In the present study we used SERT homozygote knockout rats to examine the putative role of SERT in female sexual behavior. The homozygous knockout (-/-) may mimic a chronic SSRI administration situation. Female sexual behavior was measured in a paced mating procedure, in which the female is "in control". Basal sexual behavior and the effect of 8-OH-DPAT (5-HT_{1A} agonist) on this behavior were tested in all genotypes. There was no difference in sexual activity between the SERT^{+/+}, +/- and -/- rats. 8-OH-DPAT inhibited the proceptive behavior (darting, hopping) in SERT^{+/+} and +/- females, whereas this effect was only present with high doses of 8-OH-DPAT in the SERT -/- rat. There was no effect of the 5-HT_{1A} agonist on time spent with the male rat. It can be concluded that the absence of the SERT leads to adaptation mechanisms in 5-HT neurotransmission. The lower activity of 8-OH-DPAT to inhibit sexual behavior suggests that 5-HT_{1A} receptors have been desensitized.

KEYWORDS

Serotonin transporter knockout rat, sexual behavior, 8-OH-DPAT, females

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TITLE**THE RELATION BETWEEN ATTAINMENT OF MOTOR MILESTONES AND VOLUMETRIC BRAIN MEASURES IN HEALTHY 9-YEAR OLD TWINS****AUTHORS**

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ABSTRACT

Delayed attainment of motor milestones has been suggested to act as a predictor for psychiatric illnesses at a later age (Jones, et al., 1994, *Lancet*). In healthy adults an association was found between delayed attainment of motor milestones and decreased grey matter volumes in premotor cortex, striatum, and cerebellum (Ridler, et al., 2006, *PNAS*). It is of interest to explore whether this negative association can already be found in healthy children. Therefore, we explored the association between the attainment of motor milestones and volumetric brain measures at 9-years of age in healthy children.

A total of 112 twin pairs were recruited from the Netherlands Twins Register (NTR, VU Amsterdam) at the age of 9 years for an ongoing study, including a structural MRI. Total brain, cerebellum, cerebrum and white and grey matter volumes were assessed. The twins had an average birth weight of 2598 mg and pregnancy duration of 37 weeks (N=218) reported by the parents after birth. The attainment of motor milestones (months) was previously reported by the parents when the children were 2 years old by posted questionnaires and included sitting without support, hands and knees crawling, turn from back to belly, standing without support, and walking without support. Data are currently analysed.

KEY WORDS

Motor milestones, MRI, twin study

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TITLE

THE USE OF FUNCTIONAL TRANSCRANIAL DOPPLER ULTRASOUND FOR THE ASSESSMENT OF LANGUAGE LATERALIZATION. A COMPARISON WITH FUNCTIONAL MRI

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ABSTRACT

For the measurement of language lateralization, the Intra-carotid Amobarbital Procedure (IAP) remains the golden standard. Due to its invasiveness, this procedure is restricted to patients undergoing epilepsy surgery. However, newer, non-invasive techniques such as functional MRI (fMRI) and functional Transcranial Doppler (fTCD) allow for cerebral lateralization research in healthy subjects. Lateralization indices (LIs) measured with fTCD well as lateralization indices measured with fMRI have been shown to be highly correlated with those measured by the IAP. However, only one study in a small number of subjects investigated the correlation between lateralization indices measured by fTCD and fMRI, also showing a high correlate. To further investigate the relation between LIs measured with fTCD and fMRI, we compared LIs of 12 left and 10 right-handed subjects using the exact same Word Generation paradigm for the fTCD as well as the fMRI experiment. LIs measured with fTCD were highly correlated with LIs measured with fMRI (spearman's $\rho=0.75$, $p<0.001$). We argue that fTCD is indeed a useful tool for the measurement of language lateralization, especially for higher numbers of subjects.

KEY WORDS:

fMRI; fTCD; laterality

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TITLE
THE GABA_AR SUBUNIT A1 IS INVOLVED IN BUT NOT ESSENTIAL FOR OCULAR DOMINANCE PLASTICITY

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ABSTRACT

Critical period (CP) plasticity of the mouse visual cortex occurs around week 4-5 of development. When one eye is closed during the CP, the cortex becomes more responsive to the open eye relative to the closed eye. This ocular dominance (OD) shift in responsiveness is absent in the pre- and post critical period. Timing of the CP is regulated by the maturation of the GABAergic inhibitory system which acts by parvalbumin (PV) positive perisomatic innervation onto postsynaptic $\alpha 1$ subunit containing GABA_A receptors.

Previous literature, involving the use of benzodiazepines, suggested the $\alpha 1$ subunit of GABA_AR to be essential in the CP plasticity of the visual cortex.

With *in vivo* intrinsic optical imaging in a knock-out line for $\alpha 1$, we measured ocular dominance plasticity and acuity in the cortex to see if $\alpha 1$ was necessary to open the critical period. We show that $\alpha 1$ subunit is not essential for CP plasticity by inducing a reduced OD shift after monocular deprivation in KO mice, compared to WT mice. PV positive inhibitory innervation of layer II-III pyramidal cells is still present in $\alpha 1$ KO mice, but whether the quantity of perisomatic puncta is different compared to WT mice is currently under investigation. We are focusing on elucidating whether the change in CP plasticity is caused by a difference in timing of the CP, or by a functional change of the GABA_A receptor.

KEY WORDS

Critical period, ocular dominance plasticity, inhibitory, GABA_A receptor, $\alpha 1$

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TITLE
DYNAMIC DEVELOPMENT OF THE CALYX OF HELD

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ABSTRACT

The calyx of Held is probably the largest synaptic terminal in the brain, forming a unique one-to-one connection in the auditory ventral brainstem. During early development, calyces have many collaterals, whose function is unknown. Using electrophysiological recordings and fast-calcium imaging in brain slices, we demonstrate that these collaterals are involved in synaptic transmission. We show evidence that the collaterals are pruned and that the pruning already begins 1 week before the onset of hearing. Using two-photon microscopy to image the calyx of Held in neonate rats, we report evidence that both axons and nascent calyces are structurally dynamic, showing the formation, elimination, extension, or retraction of up to 65% of their collaterals within 1 hour. The observed dynamic behavior of axons may add flexibility in the choice of postsynaptic partners and thereby contribute to ensuring that each principal cell eventually is contacted by a single calyx of Held. New experiments aimed at addressing long-term dynamics, suggest that the Calyx of Held forms within a time window of 8 hours.

KEY WORDS

Calyx, Held, dynamics

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TITLE**TRAK PROTEINS REGULATE TRAFFICKING OF MITOCHONDRIA IN NEURONS****AUTHORS**

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ABSTRACT

The cellular transport of mitochondria to meet local energy needs is especially critical in neurons. Mitochondria are produced in the cell body, which is a long distance away from energy demanding growth cone or synapse. In neurons, synaptic activity and growth cone activity controls the motility and distribution of mitochondria. Proper localization of mitochondria is essential for the support of synapses and the outgrowth of axons and dendrites. Microtubule based transport by kinesins and dynein are primarily responsible for the transport of mitochondria towards these structures. Neurological and neurodegenerative diseases are often the result of deregulation of mitochondria transport.

Recently, *milton* was discovered in *Drosophila*, where the protein functions as an adapter molecule of kinesin-1 involved in mitochondria trafficking. Mammals express two different *milton* orthologues, named trafficking protein, kinesin binding 1 and 2 (TRAK1 and TRAK2). It has been shown that *milton*/TRAK connects kinesin-1 to the mitochondrial membrane via the Rho-like GTPase, miro. In this model, kinesin-1, *milton*/TRAK and miro work together to transport mitochondria. However, the role of TRAK has not been investigated in the mammalian nervous system. Both TRAK1 and TRAK2 localize to mitochondria in neuronal cells and are present in dendrites, cell body and axon. However, TRAK1 is predominantly present at the cell periphery while TRAK2 is expressed in the perinuclear region of the cell. To characterize the difference between TRAK1 and TRAK2, we used the microtubule-dependent-cargo relocalization assay (Hoogenraad et al., EMBO J., 2003). The data suggest that the TRAK proteins have a different effect on mitochondria distribution, most likely caused by the different affinity for kinesin-1. Since *milton*/TRAK has been shown to compete directly with light chains to bind kinesin-1, we now study the role of kinesin light chain in the regulation of TRAK binding to kinesin-1. Ultimately, we aim to investigate how TRAK proteins can achieve specificity, directionality, and temporal control of mitochondrial transport in the mammalian nervous system.

KEY WORDS:

Mitochondria, intracellular trafficking

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TITLE**INNATE AND ADAPTIVE IMMUNITY IN AMYOTROPHIC LATERAL SCLEROSIS (ALS):
EVIDENCE OF COMPLEMENT ACTIVATION****AUTHORS**

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ABSTRACT**Background**

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by loss of motor neurons and gliosis in motor cortex (MCx) and spinal cord (SC). Although the etiology of ALS is still unclear, recent evidence suggests a role for the immune system in the disease process.

Objective

To analyze the presence and distribution of inflammatory cells, such as microglia/macrophages and T lymphocytes as well as components of the complement system in sporadic and familial ALS cases.

Methods

We investigated the distribution of cellular components of innate and adaptive immunity using immunohistochemistry on SC and MCx sections of both sporadic (n= 16; sALS) and familial (n= 4; with frontotemporal dementia; FTD-ALS) ALS cases. We analyzed the expression and cellular distribution of complement components as well. Quantification was performed for all stainings.

Results

In all ALS cases a prominent presence of microglial cells expressing class II-antigens (HLA-DR) and CD68-positive macrophages was found in both SC (ventral horn and corticospinal tracts) and MCx. We also observed perivascular and parenchymal T-lymphocytes (CD3⁺; with a predominance of CD8⁺ T-cytotoxic/suppressor cells) and the presence of dendritic cells (DCs; DC-SIGN⁺). Quantitative analysis showed a significantly higher number of HLA-DR⁺, CD68⁺, CD3⁺, CD8⁺ cells and DCs in ALS SC and MCx compared to control tissues. The number of microglia/macrophages and T-lymphocytes was higher in long term sALS patients as compared to sALS patients with rapid ALS progression. In contrast DCs were more prominently observed in patients who had a more rapid progression. Several components of the complement cascade (C1q, C3c and C3d) were observed in active microglia and reactive astrocytes in SC and MCx of ALS patients.

Conclusions

Our findings demonstrate a persistent activation of immune/inflammatory responses in ALS, including the activation of the complement system. Understanding the role of complement activation in motor neuron degeneration in ALS may be of great importance in the development of new therapeutic strategies.

KEY WORDS

ALS, immunity, complement, neurodegeneration

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TITLE

L-2-HYDROXYGLUTARIC ACIDURIA: PATTERN OF MRI ABNORMALITIES IN 53 PATIENTS

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ABSTRACT

Introduction. L-2-hydroxyglutaric aciduria (L2HGA) is a rare neurometabolic disorder with an autosomal recessive mode of inheritance. Clinically, affected individuals have only neurological manifestations consisting of mild to moderate psychomotor retardation, cerebellar ataxia, macrocephaly, and epilepsy. Biochemically, affected individuals have elevated levels of L-2-hydroxyglutarate in their urine. MRI demonstrates a rather consistent pattern of signal abnormality of subcortical white matter, cerebellar atrophy, and signal abnormalities in the basal ganglia. However, the details of this pattern have not been confirmed using a standard protocol for reviewing MR images. Furthermore, the course of the MRI abnormalities over time has not been explored.

Material and methods. We retrospectively reviewed the MRIs of 53 patients with genetically confirmed L-2-hydroxyglutaric aciduria. The MRIs were sent to us by many different centers and, consequently, different pulse sequences had been used. However, at least a complete series of transverse T2-weighted images was available for every patient. The images were reviewed according to a previously established scoring list. The scoring of the MRI abnormalities was related to the disease duration. Statistical analyses (independent samples t-test/one-way ANOVA) were performed to assess the MRI course of L2HGA. A P-value of less than 0.05 was considered to be evidence of a significant relationship.

Results. MRI showed that most severe white matter abnormalities were present in the directly subcortical white matter (figure 1). Central white matter structures were better preserved. The white matter changes were confluent and had a symmetrical distribution. The subcortical white matter often had a mildly swollen aspect, with broadening of gyri. In patients with longer disease duration, white matter atrophy could be present with dilatation of the lateral ventricles and subarachnoid spaces (table 1). Bilateral involvement of the globus pallidus and the caudate nucleus was invariably seen (figure 1). The thalamus was rarely involved. The cerebellar white matter was never affected, but bilateral involvement of the dentate nucleus was present in all patients (figure 1). Cerebellar atrophy was seen in some patients.

Table 2 Pattern of MRI abnormalities in L2HGA

| MR imaging abnormalities | |
|--------------------------|--|
| White matter | Frontal, subcortical preference External/extreme capsule abn. |
| Aspect of white matter | Multifocal or confluent lesions Symmetrical lesions |
| Gray matter | Caudate nucleus abn. Putamen abn. Globus pallidus abn. Dentate nucleus abn. |
| Time course | White matter atrophy |

Discussion and Conclusions. The MRI abnormalities in L2HGA start with isolated subcortical white matter lesions in the frontal lobe. As the disease progresses the abnormalities spread to the parietal, temporal, and finally occipital lobe (antero-posterior progression). Part of the central white matter also becomes involved (centripetal progression). The corpus callosum, internal capsule and brainstem are spared in all stages. Furthermore, the initially isolated lesions merge to yield a more confluent aspect. Over time white matter atrophy occurs.

Table 2 summarizes the pattern of MRI abnormalities. The most specific abnormality is the bilateral involvement of the dentate nuclei. In combination with subcortical white matter changes the differential diagnosis mainly consists of Canavan Disease

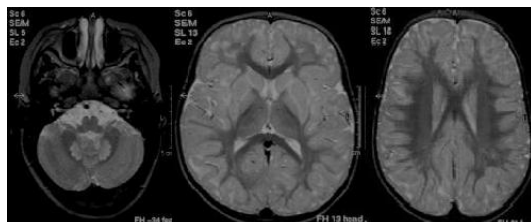


Figure 1 T2-weighted images of a patient with L2-HGA

Table 1 MRI abnormalities in L2-HGA over time

| MRI abnormality | | Number of Patients | Mean duration (years) | σ |
|---------------------|---------------|--------------------|-----------------------|----------|
| Preference WM | Subcortical | 29 | 6.7 | 0.003 |
| | Subc+Central | 14 | 13.8 | |
| Preference Lobe | Frontal | 23 | 6.3 | 0.016 |
| | Fron+Temp/Par | 7 | 9.3 | |
| | Global | 13 | 13.7 | |
| Isolated WM lesions | Absent | 18 | 12.1 | 0.02 |
| | Present | 25 | 6.7 | |
| Confluence lesions | Frontal | 9 | 7.2 | 0.059 |
| | Fron+Temp/Par | 15 | 6.2 | |
| | Global | 19 | 12.1 | |
| WM atrophy | Absent | 30 | 6.9 | 0.005 |
| | Present | 13 | 13.7 | |

KEY WORDS: MRI, leukencephalopathy, metabolic disorder, child neurology

TITLE
ELECTRO-ACOUSTIC STIMULATION IN THE COCHLEA OF PARTIALLY DEAFENED GUINEA PIGS

AUTHORS

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ABSTRACT

A cochlear implant is a device that is used in subjects with severe to profound hearing loss. The cochlear implant stimulates the auditory nerve electrically, thereby generating auditory sensations. The criteria for implantation with a cochlear implant are nowadays relaxed, and patients with considerable acoustic low-frequency hearing are implanted. These patients thus combine low-frequency acoustic hearing with electric high-frequency hearing. Preservation of residual hearing in the implanted ear improves speech intelligibility and increases the esthetic value of sound after implantation. We assume that residual low-frequency hearing has optimal beneficial effects in cochlear implant patients when interactions of electrical stimulation on the acoustic responses in the cochlea are minimal. In this study we investigated the effects of ipsilateral intracochlear electrical stimulation on the acoustically evoked compound action potential (CAP) in normal-hearing and partially deafened guinea pigs. The stimulation electrode was placed in the basal turn (i.e. the high frequency region) of the cochlea via a cochleostomy. The return electrode was placed on the basal turn of the cochlea.

Animals were partially deafened using a kanamycin and furosemide co-treatment. CAP thresholds of partially deafened animals increased from low to high frequencies. CAP thresholds at 0.5 and 1 kHz were nearly normal, whereas the threshold at 8-16 kHz was increased with ~60 dB. In line with this finding, the loss of hair cells in deafened cochleas increased from apical to basal cochlear regions. After deafening a short (2 weeks), or long (10 weeks) post-treatment interval was applied. After a 10 week interval the number of spiral ganglion cells was reduced in the basal turn, whereas after a 2 week interval the number of spiral ganglion cells was comparable to that in normal-hearing animals.

Electrical stimulation suppressed high frequency-evoked CAPs in normal-hearing animals. Low-frequency-evoked CAPs were hardly affected in hearing and partially deafened animals. Preliminary data show similar results in both groups of partially deafened animals.

These data support the view that the cochlea can be electrically stimulated in a place-dependent manner, and that high-frequency cochlear regions can be stimulated electrically without affecting low-frequency acoustical hearing.

Acknowledgement

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KEY WORDS

Cochlear implant, compound action potential, guinea pig, residual hearing

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TITLE
RILUZOLE TREATMENT IN THE MARMOSET MPTP MODEL

AUTHOR(S)

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ABSTRACT

The sodium channel blocker Riluzole has neuroprotective properties in amyotrophic lateral sclerosis (ALS) and has proven to be neuroprotective in a model for Parkinson's disease (PD). The present study determines the neuroprotective effect of Riluzole in the marmoset MPTP (1-methyl-1,2,3,6-tetrahydropyridine) model for PD on different behavioral and physiological parameters. In this study 18 marmoset monkeys were used to evaluate the effect of Riluzole on MPTP intoxication. Twelve marmosets were treated with a moderate total dose of MPTP (7 mg/kg in two weeks). Six of these twelve marmosets received Riluzole twice daily (orally 10 mg/kg) from one week before MPTP intoxication up to one week after the last MPTP injection, the other remaining twelve monkeys received vehicle twice daily. The animals home cage behavior was scored daily (clinical score and abnormal involuntary movement scale) and once a week the animals were tested for locomotor activity, hand-eye coordination, jumping behavior and turning ability. Three weeks after MPTP intoxication the animals were sacrificed and substantia nigra was fixed with 4% paraformaldehyde and imbedded in paraffin for TH immunohistochemical staining on dopaminergic neurons. All MPTP treated marmosets were affected on all behavioral parameters. Riluzole improved some of the behavioral parameters: clinical score, AIMS, hand-eye coordination and turning ability were significantly improved. In contrast, locomotor activity and jumping ability were not positively affected by Riluzole. The number of the TH expressing cells still has to be evaluated and results will be presented on the poster. The present data suggest that Riluzole prevents the decrease of specific movement-related behavior after MPTP intoxication. The compound might be used as a protective therapy to maintain patients' functional abilities in the early phase of PD, probably by preserving dopaminergic neurons in a more or less healthy state.

KEY WORDS

Riluzole, MPTP, marmoset, neuroprotection, behaviour, TH

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TITLE

MEASURING THE EFFECTS OF ENVIRONMENTAL ENRICHMENT ON VISUAL PLASTICITY OF ADULT MICE BY *IN VIVO* CALCIUM IMAGING.

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ABSTRACT

Most neurons in the primary visual cortex (V1) are more responsive to stimuli from one eye than from the other. This preferred responsiveness is strongly influenced by visual experience during postnatal development. When during a critical period of development one eye is deprived for example, responsiveness of V1 to the deprived eye decreases while that of the non-deprived eye increases, resulting in a so called **shift of ocular dominance**. The loss of responsiveness in the deprived eye is accompanied by a reduction in visual acuity. This form of ocular dominance plasticity is confined to the critical period, but when mice are reared in the dark this critical period is postponed and initiated as soon as light hits the retinas. Interestingly, in adult mice (P60-P120) but not in adult cats or monkeys, a residual shift has been observed. One possibility is that the critical period in mice never really terminates because of the lack of visual stimuli available during standard laboratory housing, a situation similar to although not as severe as dark rearing. We hypothesized that if this is the case environmental enrichment in adult mice could reduce critical period plasticity. First, this possibility was examined with intrinsic optical imaging and indeed enriched mice showed a much smaller ocular dominance shift, compared to standard housed mice. Furthermore, we observed a significant increase in signal strength in enriched mice, possibly due to angiogenesis. To further examine this we would now like to use ***in vivo* calcium imaging** using OGB1-AM which allows us to see whether neurons have become more responsive in enriched mice, and possibly will reveal if more refined retinotopic and acuity maps are formed in these mice.

KEY WORDS:

Adult visual plasticity, ocular dominance, *in vivo* calcium imaging

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TITLE**SUBREGIONS IN THE FRONTAL EYE FIELDS PROJECTING TO THE SUPERIOR COLLICULUS ARE CRUCIAL IN MAKING ANTI-SACCADES: AN FMRI-DTI STUDY****AUTHORS**

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ABSTRACT**Introduction**

Besides directly controlling behavioral output, almost all cortical areas in the vertebrate brain take part in recurrent connections through the subcortical basal ganglia nuclei, through parallel inhibitory and excitatory loops. It has been suggested that these circuits can modulate our reactions to external events, such that appropriate reactions are chosen from many available options, thereby imposing volitional control over behavior.

The saccade system provides an excellent model to test this general basal ganglia functionality. Here, we use the anti-saccade task to probe our ability to overcome automatic reactions, and instead impose volitional control over movements.

Almost all available knowledge of this system is obtained from animal studies. We intended to study the role of the direct oculomotor control pathway (frontal eye fields (FEF) – superior colliculus (SC)) and indirect pathway through the basal ganglia (FEF – caudate nucleus (CN) – substantia nigra - SC) in suppressing or allowing automatic reactions to appearing stimuli in human subjects. We studied the connections between these areas with a combination of functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). Endpoints from fibers projecting from SC and CN might target different parts of the FEF. This differentiation in FEF projection areas allows specific investigation of the output of FEF to basal ganglia or directly to SC when automatic reactions are to be suppressed or not.

Methods

15 subjects had to perform a pro-anti saccade task over 4 fMRI sessions. One session was a block design with a pro- or anti saccade every 2s. This design allowed robust individual localization of the FEF. The three other sessions constituted an 8 minute event-related design, with 8s between consecutive pro- or anti-saccades. A DTI scan was made for reconstruction of the white matter tracts. The CN and SC served as starting regions for fibertracking. Voxels in the FEF as localized with the fMRI block design were classified to 3 'projection classes': to ipsilateral CN, SC or both. When a voxel was within 10mm from an ipsilateral fiber endpoint, it was marked as belonging to a projection class. FEF-voxels connected to both CN and SC were excluded from further analyses. This resulted in two unique voxel subpopulations for left and right FEF: projecting to ipsilateral SC or CN. From the event-related data a peristimulus time histogram (PSTH), after target onset, was extracted for each different voxel class.

Results

We found different unique voxel populations for both projections in the FEF in 11 subjects. In general, FEF-voxels tended to show a higher BOLD signal in anti-saccade condition compared to pro-saccade condition.

During anti-saccades, contralateral FEF-voxels projecting to the SC showed a higher activation compared to FEF-CN voxels after 4s, around the peak of a standard hemodynamic response curve.

Conclusion

These findings suggest that an increase in activity in the contralateral FEF-SC projection is crucial for making an anti-saccade and not an increase in the contralateral FEF-CN projection or inhibition in the ipsilateral FEF-CN projection. The FEF-CN projections might therefore merely have a gating function.

KEY WORDS

Frontal eye fields, superior colliculus, caudate nucleus, anti saccades, basal ganglia, fMRI, DTI

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TITLE**CHARACTERIZING THE FUNCTION OF NEUROPILIN 1 AND 2 IN THE INTERACTION BETWEEN MENINGEAL AND SCHWANN CELLS****AUTHORS**

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ABSTRACT

Transplanted Schwann cells (SCs) derived from peripheral nerves can enhance axonal regeneration in spinal cord injuries. SCs interact poorly with meningeal fibroblasts (MCs) and reactive astrocytes which are present in the scar. Injured spinal cord axons usually grow along transplanted SCs but are inhibited in their growth at astrocyte/SC and SC/MC boundaries. It is known that MCs express class 3 semaphorins (Semas), secreted chemorepulsive guidance cues, and that their receptors, Neuropilin 1 (Npn1) and 2 (Npn2), are expressed by SCs. In this study we aim to characterize the function of Npn1 and Npn2 in SCs *in vitro*. We hypothesize that Npns and Semas play a major role in the limited interaction of SCs and MCs in the glial-fibrotic scar. Expression patterns of class 3 Semas and Npns in cultured MCs and SCs were characterized using qPCR and immunocytochemistry. Both MCs and SCs express Npns and class 3 Semas. Sema3A, Sema3C, Sema3E and Sema3F have relative high mRNA expression in MCs, while Sema3B, Sema3C and Sema3E have relative high expression in SCs. Knockdown of Npn2 expression in SCs leads to a 42% decrease of SC cluster formation in SC/MC co-cultures. Conditioned medium from MCs causes increased clustering of SCs. Our results show that the interaction between SCs and MCs is improved when the Sema receptor Npn2 is downregulated but presently the exact mechanism by which this is achieved remains elusive.

KEY WORDS

Meningeal cells, neuropilins, neuroregeneration, Schwann cells, semaphorins

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TITLE**DIFFERENTIAL EFFECTS OF THE CB1 RECEPTOR ANTAGONIST SR141716A AND THE FAAH-INHIBITOR URB597 IN THE 5-CHOICE SERIAL REACTION TIME TASK****AUTHORS**Joost Wiskerke*, D. Schetters, A.N.M. Schoffelmeer, T. Pattij**DEPARTMENT/INSTITUTE**

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ABSTRACT

Previously, we showed that in the 5-choice serial reaction time task (5-CSRTT), a rodent model for measuring attention and motor impulsivity, a systemic injection of the cannabinoid 1 (CB1) receptor antagonist SR141716A (0.3-3mg/kg) dose-dependently reduced impulsive behavior and slightly improved attentional functioning, but only at lower concentrations [Pattij et al. 2007, *Psychopharmacology* 193]. In contrast, SR141716A did not affect another form of impulsivity, impulsive choice, as measured in a delayed reward paradigm. Here, we attempted to further characterize the role of CB1 activation in motor impulsivity by studying the effects of systemic injections of SR141716A and URB597, an inhibitor of the enzyme fatty acid amide hydrolase (FAAH) which is responsible for the hydrolysis of the endocannabinoid anandamide, in the 5-CSRTT. The effects of these compounds were tested both under standard baseline conditions (intertrial interval (ITI) = 5 seconds) as well as after prolonging the ITI duration to 7 seconds, a manipulation known to elevate impulsivity by increasing the number of premature responses. Results show that the CB1 antagonist SR141716A (1 mg/kg) partially blocked the effects of increased impulsivity by lengthening the ITI duration, without affecting attentional functioning. In contrast, the FAAH inhibitor URB597 (0.025-0.5 mg/kg) did not affect premature responding under any of the conditions tested. However, at lower doses, URB597 slightly impaired attentional functioning, but only when the ITI duration was 5 seconds. Together, these data indicate that CB1 activation is involved in mediating motor impulsivity, but that this activation is likely not due to release of anandamide. Future studies in our laboratory will therefore focus on the role of the endocannabinoid 2-AG in motor impulsivity.

KEY WORDS

Impulsivity, cannabinoid system, 5-choice serial reaction time task, CB1 receptor

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TITLE
MITOCHONDRIAL ALTERATIONS IN MS LESIONS

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, characterized by demyelination and neurodegeneration. Although MS pathogenesis is not completely understood, several studies suggest that mitochondrial dysfunction and subsequent free radical production play important roles in MS lesion development and progression. In MS lesions, mitochondrial dysfunction is thought to occur as a response to demyelination and inflammation, since demyelination raises the energy demand in axons, thereby affecting number, distribution and activity of mitochondria. In this study we have investigated the distribution of mitochondria and mitochondrial enzyme activity in various MS lesion stages by (immuno)histochemical and biochemical techniques. We have quantitatively assessed the number of mitochondria and their co-localization with axons and astrocytes within MS lesions and adjacent normal appearing white matter (NAWM). We observed a significant increase in the number of mitochondria in MS lesions. The activity of complex IV is strikingly upregulated in MS lesions compared to control white matter and, to a lesser extent, NAWM. Upregulation of complex IV activity and enhanced numbers of mitochondria were observed in axons and astrocytes. To unravel the functional role of enhanced mitochondrial activity in astrocytes we isolated primary astrocytes from NAWM and MS lesions. Astrocytes were probed with JC-1 and MitoTracker Red CM-H₂Xros, to detect mitochondrial membrane potential and mitochondrial H₂O₂ production, respectively. Mitochondrial membrane potential was found to be decreased in MS lesion derived astrocytes, whereas mitochondrial H₂O₂ production was increased. Finally, we demonstrate increased expression of the mitochondrial stress protein mtHSP70 in MS lesions, indicating the occurrence of ongoing mitochondrial oxidative stress. Enhanced mitochondrial numbers in MS lesions might contribute to ROS formation and subsequent axonal damage. Furthermore, our data indicate that lesional astrocytes might be involved in neurodegeneration through increased ROS production.

KEY WORDS

Multiple sclerosis, mitochondria, oxidative stress, astrocytes

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TITLE**A LOOK INSIDE CEREBELLAR CORTICAL NEURONS: LINKING ELECTROPHYSIOLOGY TO MORPHOLOGY****AUTHORS**

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ABSTRACT

Neuronal activity *in-vivo* is mainly recorded with the use of extracellular techniques, which do not allow control over the neuron or the recording of subthreshold phenomena such as EPSPs, IPSPs and cell-specific currents. Whole-cell patch-clamp recordings can overcome these limitations and enable us to observe other aspects of the cell's physiology in addition to the spike output.

In this study we performed blind whole-cell recordings of various cell-types in the cerebellar cortex of ketamine-xylazine anesthetized mice. Recorded cells were clustered on the basis of their electrophysiological properties, including input resistance, capacitance and spontaneous activity. Clusters were subsequently identified via histological recovery and identification of stained neurons. We found all four common clusters of neuronal types: Purkinje cells, granule cells, molecular layer interneurons and Golgi cells.

Purkinje cells showed characteristic complex and simple spike firing. Periods of depolarized membrane potential were interrupted with periods of hyperpolarized membrane potential. These so-called up- and down-states were observable in a large fraction of Purkinje cells recorded under anesthesia. Granule cells fired few spontaneous spikes and were characterized by small size and high input resistance. Molecular layer interneurons had a low input resistance and showed subthreshold membrane potential oscillations with low frequency. Capacitance in these cells was considerably larger than in granule cells. Input resistances measured in Golgi cells were intermediate. Golgi cells had a capacitance comparable to molecular layer interneurons. Thus our *in-vivo* patch-clamp recordings allow us to electrophysiologically distinguish the major cell types in the cerebellar cortex. These experiments, therefore, make it possible to investigate the properties of these neurons in greater detail and ultimately in relation to behavior in awake animals.

KEY WORDS

Cerebellum, *in-vivo*, patch-clamp, electrophysiology

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TITLE

UP AND DOWN WITH TMS AND EEG: DISCRIMINATING DISRUPTION OF FIGURE GROUND SEGREGATION SIGNALS IN EARLY VISUAL AREAS

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ABSTRACT

In figure-ground segregation two processes can be discriminated: boundary detection and surface segregation. The neural origin and temporal dynamics of these two processes is still much disputed. In monkey V1 neural correlates of surface boundary detection have been found, but there is still much debate about whether surface segregation signals can be found in human V1.

It has been proposed that boundary detection is mediated by feed forward activations and lateral interactions whereas surface segregation (denoting an area as figure or ground) requires recurrent processing. In previous studies correlational measures were used. To causally examine the role of recurrent processing in figure-ground segregation and to test whether boundary detection and surface segregation processes can be discerned as two temporally distinct processes that can be located in early visual areas we administered TMS stimulation to early visual areas in different time intervals from stimulus onset while recording EEG. In order to differentiate between neural correlates of boundary detection and surface segregation we used a paradigm that dissociates between boundary detection and surface segregation.

To overcome the artifacts created by combining TMS with EEG we had to create a procedure to correct the distorted EEG signal in combination with hardware that does not 'clip' when a TMS pulse is applied and special hardware. Together with (preliminary) results from our TMS/EEG experiment on figure-ground segregation in early visual areas, the artifact correction procedure will be fully described.

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TITLE
OPERANT ALCOHOL SELF-ADMINISTRATION AND FIVE-CHOICE REACTION TIME TASK PERFORMANCE IN WISTAR RATS EXPOSED TO CHRONIC ALCOHOL DURING ADOLESCENCE

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ABSTRACT

Adolescence is a transition phase that can be characterized by increased risk taking, increased novelty seeking and intensified peer relationships in both humans and rats. These behavioral changes are accompanied development of prefrontal cortex and hippocampus, extensive synaptic pruning throughout the brain, and maturation of several neurotransmitters and receptors towards adult levels and subunit composition.

Adolescence is also often the age of onset of alcohol use. In the last two decades an alarming trend is seen of increased alcohol intake among youth in this unique developmental period. As alcohol is known to affect many of the changing neurological systems it is important to investigate the effect of adolescent alcohol use on adult behavior. The present study was designed to investigate the effects of adolescent alcohol exposure on disturbances in motivational and cognitive behavior in later life as assessed by operant alcohol self-administration (SA) and five-choice serial reaction time task (5CSRTT) performance.

Male Wistar rats were exposed to either water/water, water/ 0.2% saccharin, or 10% alcohol /0,2% saccharin in a two bottle free choice paradigm during either postnatal day (PND) 34-43 (peri-adolescents) or PND 60-69 (post-adolescents). Ethanol intake was between 3-6 g/kg/day. At adult age, 91 days after the last treatment day, rats were either trained to self administer a 10% alcohol solution (EXP1) or on 5CSRTT performance (EXP2).

Exp1: All groups acquired SA at the same pace and no difference was found in performance during between session progressive ratio or extinction training. A cue-induced relapse test revealed a borderline significant reduction of reinstatement in alcohol treated peri group compared to water treated animals.

Exp2: No treatment effects were found on baseline performance in the 5CSRTT. However, a reduced correct response latency in post-adolescent treated animals compared to peri-adolescent animals was observed.

A history of chronic alcohol exposure during adolescence had no effect on acquisition, motivation, extinction and reinstatement of operant self administration of adult Wistar rats or on performance in 5CSRTT. The age related effect on response latency might be attributed to differences in neurobiology at time of treatment.

Adolescent binge-like alcohol exposure has been reported to have more detrimental behavioural effects than chronic exposure. Therefore, effects of adolescent binge-like exposure on SA and 5CSRTT performance need to be assessed.

KEY WORDS

Behaviour, addiction, alcohol, adolescence, rat

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TITLE
BRAIN ACTIVATION DURING MENTAL ROTATION IN TRANSSEXUAL ADOLESCENTS: AN FMRI STUDY

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ABSTRACT

The VUmc gender team for children and adolescents assesses early-onset transsexuals on a regular basis. Little is known about aetiological aspects of transsexualism. Sex differences in cognition, gender identity and sexual orientation may all reflect sex-related neuroanatomical differences in the human brain. In transsexual people a reversal of the sex difference in the Bed Nucleus of the Stria Terminalis has been observed.

We hypothesize that in early-onset transsexualism the brain develops to some extent in the direction of the desired sex. The present study focuses on brain activation and performance during a cognitive task known to reflect sex differences. Mental rotation tasks appear to produce the most robust sex differences among all neuropsychological tests. Mental rotation is a complex cognitive skill depending on the manipulation of mental representations. Neuroimaging studies have consistently reported activation of the parietal cortex during performance on mental rotation tasks.

We present data from an fMRI study on mental rotation using an adapted version of the 3D mental rotation test of Vandenberg and Kuse. Colored drawings were presented pair wise. In half of the trials the 3D shapes were congruent but portrayed with different orientation, in the other half the shapes were incongruent. A single 3D figure with an arrow beneath was presented as control image.

We included 9 male-to-female adolescents (mean age 16.5 years) before the start of their hormone treatment and 9 (mean age 17.5 years) after one year of estrogen treatment, and 8 female-to-male adolescents (mean age 18.1 years) before the start of the testosterone treatment and 11 (mean age 18.3 years) after one year of treatment. In addition 20 non transsexual female (mean age 17.3 year) and 13 male controls (mean age 18.1 years) were included in this study.

Magnetic resonance imaging (MRI) included a coronal 3D gradient-echo T2-weighted sequence (matrix 256 x 256, voxel size 3 x 3 x 3 mm, 35 sections) for functional MRI and was performed on a Philips Intera 3.0 Tesla with a standard 8-channel head coil.

Analysis of response accuracy and reaction times revealed sex differences between control males and females in advantage of the males. The transsexual adolescents showed both performance and reaction times in accordance with the desired sex. Activation data during mental rotation will be shown.

KEY WORDS

Transsexualism, functional MRI, mental rotation, adolescents

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TITLE**STRAIN DIFFERENCES IN PASSIVE AVOIDANCE EXTINCTION IN MICE****AUTHORS**Ji Un Youn, Steven van Huiden, Matthijs Verhage, Oliver Stiedl**DEPARTMENT/INSTITUTE**

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ABSTRACT

The experience of a traumatic event is not uncommon in our life. However, only a small percentage of people exposed to an extreme stressor develop posttraumatic stress disorder (PTSD). This suggests that individual difference regarding the vulnerability and resilience plays an important role in the development of PTSD. Although a few twin studies reported a strong genetic component of the disorder, the underlying interaction between gene and environment has still been elusive. In the present study, we aimed to model the individual difference in the most commonly used inbred mouse strain C57BL/6J and the C57BL/6N substrain. Previous studies reported that C57BL/6J mice show similar fear response but slower fear extinction compared to C57BL/6N in fear conditioning. However, fear conditioning might not be an ideal model to study PTSD because of the difficulty to dissociate inactivity from overt fear behavior such as active suppression of ongoing behavior (freezing). As an alternative, we used passive avoidance (PA) to model PTSD in mice. In the PA paradigm, the animal is given an active choice to cross over from a light to a dark chamber which was previously associated with an aversive stimulus (electric shock). This bears resemblance to a situation in humans that requires unlearning the association between a traumatic experience and the place where it occurred. As expected, C57BL/6N showed a slower extinction rate than C57BL/6J in PA. However, when mice that did not show extinction at all were excluded from the analysis, the extinction rate was comparable in the two substrains. Considering that not everyone exposed to trauma develops PTSD, this finding is strongly reminiscent of the human situation. Further investigation will include heart rate analysis to reveal potential dysregulation in autonomic function as additional PTSD-like symptom in mice.

KEY WORDS

PTSD, strain difference, passive avoidance, C57BL/6J, C57BL/6N, fear

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TITLE**STIMULATED GENE EXPRESSION PROFILES AS A BLOOD MARKER IN ANTIDEPRESSANT-NAÏVE MAJOR DEPRESSED PATIENTS****AUTHORS**

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ABSTRACT**Context**

Major Depressive Disorder (MDD) is a highly heritable disorder with high lifetime prevalence. At present, laboratory blood tests to support MDD diagnosis are not available; these blood tests could allow subclassification of patients for a better prediction of disease course and treatment outcome.

Objective

Classify MDD patients based on whole blood gene expression profiles.

Design

A classifier approach on gene expression profiles in (stimulated) blood of unmedicated patients and controls selected from the Netherlands Study of Depression and Anxiety was performed to select genes of which the expression is predictive for the disease status.

Participants

In total, 35 unmedicated, **antidepressant-naïve** MDD patients and 37 healthy controls, aged 20 to 63 years.

Setting

The Netherlands

Main outcome measure

To overcome variation in basal blood gene expression levels and to reveal quiescent differences related to disease state, we applied a powerful *ex vivo* stimulus, i.e. incubation with lipopolysaccharide (LPS; 10 ng/ml blood). Gene expression was measured using whole genome microarrays, co-hybridizing basal and *ex vivo* LPS-stimulated blood from each subject, or using quantitative polymerase chain reaction (qPCR).

Results

We identified a molecular marker set (7 genes) of MDD in 42 subjects (training set microarray) based on stimulated blood gene expression that was superior to that from genes from basal blood. The MDD-marker was confirmed in an independent validation set of 25 subjects ($P=0.011$). In addition, using an independent quantitative PCR method, subjects from both the training and the validation sets were classified according to disease state ($P=0.007$, and $P=0.019$, respectively). The MDD-marker correlated with MDD severity, suggesting predictive validity.

Conclusion

We provide first evidence to classify MDD patients based on stimulated whole blood gene expression profiles. The good sensitivity and specificity [ook in results hierboven noemen] may serve to determine the predictive value of this marker for disease course and treatment outcome.

KEY WORDS

Major depressive disorder, biomarker, gene expression, LPS

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TITLE
INHIBITORY STRUCTURES IN THE HIPPOCAMPUS

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ABSTRACT

Several lines of research have confirmed the existence of a complex structure in the hippocampus, consisting of feed-forward and feedback loops operating on different timescales. Interneurons seem to specialise in separate functions: interneurons that receive feed-forward inhibition are physically different from the ones that participate in feedback loops, and interneurons that participate in loops with fast kinetics are separate from the ones that participate in loops with slow kinetics. Moreover, the projection areas also differ between different loops. Finally, these different groups of interneurons seem to fire preferentially at different phases of ongoing rhythms, such as the theta and gamma cycle and ripples. This means that interneurons are functionally segregated. Several lines of research suggest that these separated loops are capable of influencing each other. What is the function of these segregated loops? And what does the combination of these loops result in? Computational studies have been carried out to answer these questions, showing differential roles for different types of interneurons and pyramidal cells in beta, gamma and theta oscillations. Moreover, the timing of inhibition seems to be crucial, as it can cause both phase advances and delays. Finally, the loss of slow feedback OLM cells in temporal lobe epilepsy results in decreased inhibition in pyramidal cell dendrites and increased inhibition around the soma, the result of hyperactivity of somatic projecting interneurons. The effect of these alterations is epileptiform activity. In this study we investigate the effects of several types of interneuron projections onto a pyramidal cell model as proposed by Pinsky and Rinzel.

KEY WORDS

Hippocampus, inhibition, computational neuroscience

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TITLE**DRUG-INDUCED WEIGHT GAIN: EFFECTS OF OLANZAPINE IN AN ANIMAL MODEL****AUTHORS**Esther M. van der Zwaal¹, M.C.M. Luijendijk¹, S.K. Janhunen¹, S.E. la Fleur¹, R.A.H. Adan¹**DEPARTMENT/INSTITUTE**¹Rudolf Magnus Institute for Neuroscience, Dept. Neuroscience and Pharmacology, University Medical Center Utrecht, Utrecht**ABSTRACT**

Olanzapine is an effective atypical antipsychotic drug, which unfortunately often causes significant weight gain as a side effect, as well as dyslipidemia and hyperglycemia. These side effects compromise patient compliance and increase the risk for cardiovascular disease.

Olanzapine has affinity for multiple receptors, including dopamine D2, 5-HT_{2A} and 2C, histamine H₁, alpha-adrenergic and muscarinic receptors. So far it is not completely understood which of these receptors are involved in olanzapine-induced weight gain. To enable the development of novel antipsychotics that are equally therapeutically effective but less prone to cause weight gain, it is crucial to gain insight into the mechanisms involved in olanzapine-induced weight gain.

We, therefore, developed an animal model, using male Wistar rats, to study in detail the effects of this drug on feeding, food preference, locomotor activity and body temperature.

After subchronic administration, we observed an increase in abdominal adiposity. This was accompanied by a reduction in voluntary locomotor activity in both short- and long-term studies.

Furthermore, analysis of meal patterns showed an increase in average meal size, which implies an impairment of the normal satiation process. Interestingly, although little is known about the effect of olanzapine on eating behavior in humans, an increased risk of binge eating symptoms has been reported. Therefore, this model provides promising possibilities to further investigate the mechanisms underlying olanzapine-induced weight gain.

KEY WORDS:

Olanzapine, antipsychotic-induced weight gain, feeding behavior, rat model.

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