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Abstract book

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Mutations in ADNP affect subcellular localization and protein expression

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De novo frameshift and nonsense mutations in ADNP can be identified in a substantial proportion of patients with the Helsmoortel-Van der Aa syndrome. However, up until now, correlations between the different mutations and their impact on the protein have not been studied. Here we report the effect of mutations in ADNP by means of studying the expression and subcellular localization of GFP-tagged mutant transcripts in transfected HEK293T cells. Interestingly, ADNP encloses a bipartite nuclear localization signal, indicating the importance of its presence in the nucleus, and we found patient mutations therein to stall the mutant protein within the cytoplasm. Furthermore, using immunocytochemistry, we could demonstrate co-localization of wild-type ADNP with heterochromatin. We found mutations affecting the first basic region of the NLS to mislocalize mutant ADNP protein in the cytoplasm. C-terminal mutated transcripts, on the other hand, were still shuttled to the nucleus. Of the latter, transcripts with an arrested PxVxL motif were mislocalized within the nucleus, as evidenced by only partial co-localization with the heterochromatin marker. Finally, N-terminal truncated forms of ADNP are rerouted towards cytosolic proteasomal degradation and can be rescued with the proteasome inhibitor MG132.

Our results suggest a correlation between the position of the mutations across the protein, its stability and subcellular localization. This supports a mechanistic model where mutations in ADNP alter the protein's subcellular expression pattern depending on their position, potentially resulting in distinct functional effects.

Unexpected Innovative Early Diagnosis: Premature Tooth Eruption in Cognitive/Motor Delayed ADNP-Mutated Children

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Background: Late diagnosis is a major impediment in autism spectrum disorder (ASD) management. Activity-dependent neuroprotective protein (*ADNP*) is a most frequent *de novo* mutated ASD-related gene. Adnp haploinsufficient ($Adnp^{+/-}$) mice exhibit cognitive and social deficiencies while ADNP syndrome children suffer from severe impediments e.g. intellectual disability, facial dysmorphism and autistic traits.

Aims: Identify potential early diagnostic biomarkers for ADNP syndrome.

Methods: 1] Tooth development data was collected from a questionnaire, posted on ADNP parent website (www.ADNPkids.com). 2] 2 and 5-day old mouse pup mandibles and children's dry shed teeth were scanned using Micro-computed tomography (μCT) 50 system. 3] Mouse pup's *Adnp* mRNA expression was inquired online using Allen Atlas. 4] RNAseq, real-time PCR and bioinformatics were performed on three human ADNP-mutated lymphoblastoid lines (LCLs).

Results: 44/54 ADNP-mutated children were reported with an almost full erupted dentition by one year of age. μCT of $Adnp^{+/-}$ mice revealed age-dependent dysregulation of teething with significantly smaller dental sacs and tooth buds at 5-days of age, compared to littermates. Allen atlas revealed high *Adnp* mRNA expression in the jaw area. LCLs, whole mouse embryos and mouse brains analysis identified ADNP-related dysregulation of bone/nervous system-controlling genes (e.g. *BMP1*, *BMP4* and *AKAP6*).

Conclusions: This is the first time that early teething is related to ASD. Here, we discovered premature tooth eruption as a potential early diagnostic biomarker for ADNP mutation.

Work in progress: Using the ADNP mutated LCLs we are testing additional ADNP-related markers for better understanding of ADNP activity and future biomarkers.

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Assessing the level of mutation mosaicism in the ADNP gene in autistic individuals

Assessing the level of mutation mosaicism in the ADNP gene in autistic individuals

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Autism, characterized by highly-variable qualitative impairments in social interaction and communication skills, is a poorly understood disorder. In this study, we have analyzed a form of autism that is caused by mutations in a single gene called *ADNP*. The high frequency of clustered mutations of *ADNP* at the stem-loop forming sequence reveal this sequence is a mutation hotspot – somatic mutations of this may account for clinical variations in affected individuals. The potential to form an unusual DNA structure may predispose the sequence to an underlying mutation mechanism involving a DNA repair defect following pausing of a replication fork at these hairpin structures, or during aberrant repair in non-proliferating tissues. It is not known if these *de novo* mutations in the *ADNP* gene were incurred in the parental germ line and/or post-natally through the development and growth of the affected individual. The latter might be expected to display some degree of somatic mosaicism for the mutant allele. We used Digital Droplet PCR (DD-PCR) to assess, with high-sensitivity, the levels of ADNP mutation in DNA extracted from teeth, hair root cells (similar developmental origin as neurons) and ADNP patient-derived iPSCs of autistic offspring. We have developed a novel assay with DD-PCR, which theoretically should be able to detect one mutant molecule amongst 20,000 single droplet reactions. The utility of this assay will permit the assessment of the potential contribution of somatic mutations of *ADNP*, and other genes, to autism. This could impact our ability to assess the clinical variability amongst affected individuals.

Modelling ADNP-related autism in patient-derived cellular models

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ADNP mutations have been recently associated to the SWI/SNF-related autism syndrome (hereafter ARAS, from ADNP-Related Autism Syndrome) with high penetrance. ADNP is thought to act largely as a transcription factor through the interaction with at least two critical subsets of chromatin regulators, the chromatin remodeling BAF complex, related to the SWI/SNF complex,
and the heterochromatin protein 1 (HP1) involved in repression of pericentric heterochromatin. Since the molecular pathogenesis of ADNP syndrome is not well understood, we integrated three cutting edge technologies to establish relevant cellular models of the disease and to define the gene networks altered in ADNP mutated patients. Specifically, we obtained integration-free induced Pluripotent Stem Cells (iPSCs) by reprogramming fibroblasts from a highly informative cohort of ADNP patients carrying different prevalent mutations. These lines are being engineered by Crispr/Cas9 in order to derive isogenic controls in which ADNP mutations are repaired. Mutant and control were differentiated into neural crest stem cells and mature cortical neurons, and are being profiled both at the transcriptomic and at the epigenomic level for enhancer-related histone markers. Through a new computational pipeline that integrates vast amounts of expression and epigenome data, our goal is to define the gene regulatory networks that are impaired in ARAS as a result of mutations in ADNP, and identify druggable intermediates. Along with our establishment of diseaserelevant cellular models, this work will yield new insights into this neglected disorder and autism spectrum disorders in general, providing critical tools to unravel its molecular pathogenesis.

Life without brain serotonin: characterization of a TPH2-deficient rat model

Natalia Alenina

Serotonin acts as a neurotransmitter in the central nervous system. Its synthesis in the brain is regulated by tryptophan hydroxylase 2 (TPH2). Following the discovery of TPH2 by our group, a rat with the genetic deletion in the *Tph2* gene was generated (*Tph2*$^{-/-}$) using zinc-finger nuclease technology. The 11-bp mutation in the rat *Tph2* gene led to a frameshift in the open reading frame and the formation of a premature stop codon. Consequently, TPH2 was undetectable in *Tph2*$^{-/-}$ animals, leading to nearly complete (99%) depletion of 5-HT in the brain.

Although born in a normal Mendelian ratio, *Tph2*$^{-/-}$ rats showed a visible growth retardation, in terms of size and weight, already 3-4 days after birth which persisted during the first postnatal weeks. Body weight and size of *Tph2*$^{-/-}$ rats are however normalized later in life.

Investigation of the metabolomic profile in whole blood of 15 days-old rats revealed significant differences in the metabolome of *Tph2*$^{-/-}$ animals, such as changes in ethanolamine, urea, and acetoacetic acid suggesting malnutrition hypothesis for the growth retardation phenotype, presumably due to the high metabolic rate in these animals. Indeed, body composition analysis revealed a significant decrease in fat mass in *Tph2*$^{-/-}$ pups in comparison to wild type rats. Elucidating the mechanisms underlying the growth retardation phenotype in *Tph2*$^{-/-}$ animals might yield a key finding for the development of treatments for metabolic disorders.

Generation of human induced pluripotent stem cells to clarify the role of serotonin in the pathogenesis of a neurodevelopmental disorder

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Psychiatric diseases, such as attention-deficit hyperactivity disorder (AHDH) and autism spectrum disorders (ASD), are a rising burden in our society. ADHD, also classified as neurodevelopmental disorder, is characterized by developmentally inappropriate inattention, hyperactivity and increased impulsivity. The pathogenesis of such a disease could be due to abnormalities in the development of the brain and neurotransmitters like serotonin as a regulator of neurodevelopment may play a role in these processes. One of the genes that could increase the liability to ADHD is *SLC2A3*, which encodes the glucose transporter 3 (GLUT3). To examine the role of *SLC2A3* as a risk gene for ADHD as well as its connection to the serotonergic system we generated human induced pluripotent stem cells (hiPSCs) from patients with ADHD carrying CNVs of *SLC2A3* as well as age-matched controls. Therefore, isolated fibroblasts have been infected with a non-integrative Sendai virus to generate transgene-free iPSCs. Obtained hiPSC candidate clonal cell lines have been successfully characterized by immunofluorescence staining against pluripotency-associated markers, such as SSEA4 and TRA-1-60. Furthermore, we confirmed the ability of our hiPSC lines to differentiate into cells of all three germ layers using a germ layer differentiation protocol. Additionally, we optimized our protocol for the generation of hiPSC-derived serotonergic neurons to obtain a higher percentage of this neuronal subtype. Thus, we obtained rostral hindbrain progenitors that in turn could be differentiated into a subtype of neurons displaying a serotonergic phenotype assessed by an immunofluorescence staining of specific markers, such as 5-HT and TPH2.

Behavioural characteristics of tryptophan hydroxylase 2 (TPH2) - deficient rats

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Tryptophan hydroxylase-2 (TPH2) is the rate-limiting enzyme of serotonin (5-HT) synthesis in the brain. TPH2-deficient ($TPH2^{-/-}$) rats, generated using zinc-finger nuclease technology, are completely lacking serotonin in the brain. Thus, $TPH2^{-/-}$ rats represent a useful model to understand the role of central 5-HT in the regulation of different aspects of behaviour. In the current study, we assessed the impact of brain serotonin deficiency on general exploratory activity, anxiety-like behaviours and cognitive functions.

Exploratory activity was assessed in the open field (OF). The elevated plus maze (EPM) test was used as an assay of anxiety-related behaviour. Visual recognition memory was assessed in the novel object recognition task.

$TPH2^{-/-}$ rats demonstrated decreased exploratory activity in a novel environment as compared with controls. However, they tend to spend more time in the center of the OF. The potential anxiolytic-like phenotype of $TPH2^{-/-}$ rats was also demonstrated in the EPM test. There were no differences in the ability to discriminate novel and familiar between $TPH2^{-/-}$ and $TPH2^{+/+}$. Consistent with the reduced exploratory activity, total time of object exploration was also lower in $TPH2^{-/-}$ rats.

TPH2 deficiency alters the pattern of exploratory behaviour. The potential anxiolytic-like phenotype is also suggested.

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Ethical Framework of Informed Consent and Decision-Making Capacity in Clinical Dementia Research: Highlights from the Subproject ETHICS II of Project ENSURE

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KEYWORDS:
Ethics, Dementia, dementia research, Informed consent, Decision-making capacity, Vulnerabilities, Autonomy.

Introduction: Informed consent is the most scrutinized and controversial aspect of clinical research ethics. In clinical dementia research, assessing decision-making capacity may be challenging as the nature and progress of each disease influence decision-making capacity in diverse ways. Persons with dementia represent a vulnerable population deserving special attention when developing, implementing and evaluating the informed consent process. Ethical frameworks with a pragmatic contour and implication are needed to protect vulnerable patients from potential harms and ensure their optimal participation in clinical dementia research.

Objective: To determine and ethically frame the issues that should be considered during the informed consent process in clinical dementia research.

Methods: Two intertwined phases entailing three systematic reviews (SR). SR1 will map the elements of the decision-making process pertaining clinical research in patients with dementia. This review will identify elements for capacity assessment. SR2 will provide an overview of decision-making impairments associated to diverse neurodegenerative diseases. Particular attention will be given to vulnerability categories and how these influence decision-making capacity. SR3 will focus on the identification and evaluation of instruments/strategies used to improve decision-making capacity. All reviews will follow criteria for the good conduct and reporting of SR.

Expected results: An in-depth analysis of the ethical issues of the informed consent process in clinical dementia research will be integrated and developed. Practical recommendations will be driven, including a report and a guide targeted to clinicians and researchers to select clinically useful tools/strategies that improve decision-making capacity and informed consent of persons with neurodegenerative diseases, particularly dementia.

Supportive interactions in decision making: Exploring the subjective experience of people with dementia

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Keywords: dementia, qualitative research, supported decision-making, supportive interactions, self-concept

Background and Objectives: Supporting persons with dementia (PwD) in decision-making aims at protecting their rights, maintaining their autonomy and enabling them to participate in the process as active as possible. This is applicable to decision-making processes regarding research participation in particular. To ensure that supportive interventions are tailored to the needs of PwD, it is necessary to examine how PwD perceive and evaluate these interventions.
Research Design and Methods: The present study aims at investigating how PwD perceive the interaction in enhanced consent procedures. The questions if and to what extend supportive interactions with professional health care providers influence the self-concept and self-esteem of PwD are of particular interest. Data will be collected through Problem-Centered-Interviews (PCI) with PwD and their relatives, who participate in enhanced consent procedures. The PCI combines different communication strategies and is therefore an appropriate method to be adapted to the cognitive and verbal competences and needs of PwD.
Results: After years of excluding PwD from research participation, the focus is changing and the involvement of PwD in qualitative research becomes more important. Due to the evaluation of concrete support strategies the present study will give an insight into the perception of PwD. Preliminary results will be discussed at the poster session.
Discussion and Implications: The consideration of the perspective of PwD allows to derive recommendations for the de

How does it feel like … to use a BCI?

Johannes Kögel, Ralf J. Jox, Orsolya Friedrich

Brain-Computer Interfaces are a neural technology which connects human agents and computer technology via measurements of brain activities. By means of a qualitative interview study wetry to find out what experiences users of Brain-Computer Interfaces have made with the technology. The research objective of this study exceeds gathering opinions about BCIs in terms of expectations towards the technology, advantages and disadvantages of BCIs, suggestions for improvements, and visions of future BCIs. This interview study in addition aims for first-hand information regarding operating an interface, i.e. the first person perspective of the individual being connected to and being active through and with a BCI. How does it feel like to be wired to a computer and to execute actions solely through the power of their thoughts? How does it affect their sense of agency? Do they feel responsible for actions which they do not physically perform themselves? Does operating a BCI have an impact on their autonomy? Does being a hybrid agent, i.e. operating as a human-computer unit, change their self-image or the understanding of what it means to be a human? Applying Grounded Theory Methodology to the data material, we identify categories which deem to be meaningful in the context of BCI use and put these categories into relation with each other. The results of our study aim for a better understanding of key ethical concepts like agency, autonomy, and responsibility within the context of BCI use.

Ethical, Legal, and Social Challenges of Brain-Computer Interface: Comparing Expert and Public Perspectives

Matthew Sample, Stefanie Blain-Moraes, David Rodríguez-Arias, Sebastian Sattler, Eric Racine

In this poster, we present the results of an ongoing multinational survey on public attitudes towards brain-computer interfaces (BCIs). BCI devices establish an artificial connection between a brain region and its surroundings. Researchers are increasingly interested in applying these "neuroprosthetics" to address a range of neurological disorders, including locked-in syndrome and paraplegia (Krusienski & Wolpaw 2012). These applications depend not only on their technical efficacy but also on their acceptance by potential users and by society at large. Scholars in neuroethics have speculated about the social, legal, and ethical challenges of these diverse applications (Klein et al 2015; Aas and Wasserman 2015), but the issues identified in that literature must also be validated with empirical investigation. To this end, we conducted a literature review of scholarly articles on the ethics of BCIs, identifying the dominant concerns asserted therein (i.e. personhood, stigma, empowerment, responsibility, informed consent, privacy, security, and justice). We then created a survey instrument that explains each of these issues, asking respondents to evaluate them in terms of concern, in addition to providing basic demographics. Study participants were recruited from Canada, Spain, and Germany. The survey data will be analyzed to provide comparative insight into the way BCIs might be understood in differing national-cultural contexts. Accordingly, we aim to reconnect expert ethical analysis with perspectives from members of the public, exhibiting convergences and differences. Biomedical scientists, engineers, and healthcare providers could use these findings to improve design and application of BCIs through an improved understanding of socio-cultural context.

Ethical Considerations for Deep Brain Stimulation for Alzheimer: the Importance of Methodological Rigor and Scientific Validity

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PD Dr. phil. Dipl.-Phys. Sabine Müller

Deep brain stimulation (DBS) has been investigated as potential intervention for Alzheimer's disease (AD). In order to protect participants' safety with regard to the uncertainties about unknown risk of side effects and adverse events such investigational research should adhere to highest ethical requirements and methodological rigor.[1] For this purpose, the assessment of unknown risks is best conceived on a continuum from conservative protectionism to experimental adventurism (certainty-uncertainty continuum).[2] Protectionism may impede scientific progress and can harm patients by hampering the development of new and better treatment possibilities. Because DBS involves invasive neurosurgery, it belongs to "Class III" of medical devices implying "high risks" (EU Medical Devices Regulation). The coarse classification into four classes (I, IIa, IIb and III) is unlikely to decompose the certainty-uncertainty continuum adequately into distinct categories. Due to its reversibility and minimal-invasiveness, DBS paves the way for new technologies and indications, although the ethical justification of research rationale based on conclusive evidence remains key. We recommend a linear relationship between risk and evidence: the riskier a novel approach, the higher the demands on quality criteria used to assess some research hypothesis.

To apply these theoretical considerations to empirical research, we performed a systematic ethical review of DBS for AD research.[3] The results provide hints for insufficient patient protection.[i] The major threat being a lack of preclinical evidence to inform the risk-benefit assessment, which is further complicated by patients' limitations with regard to decision-making.[ii] Therefore, several safeguards are required to better protect vulnerable participants with cognitive deficits.[iii]

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Contemporary Psychiatric Neurosurgery: Updates on a Cross-National Comparison of Trends in Media Coverage and Public Attitudes

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Understanding the exposure of patients and the public to contemporary trends in psychiatric neurosurgery is essential to understanding their views and receptivity to them. Toward this goal, we conducted an in-depth content analysis of media articles and reader comments on all types of psychiatric neurosurgery between 1960-2015. We used Factiva and media websites to compile full-length articles published in major newspapers and magazines from ERAnet consortium partners: Canada, the US, Germany, and Spain.

The final dataset comprised of 517 articles and 477 comments (Canada/USA: 201 articles, 183 comments; Germany: 156 articles, 115 comments; Spain: 160 articles, 179 comments). We coded inductively for themes and phenomena of interest. We found that coverage of psychiatric neurosurgery has increased and changed over time, although frequent references to historical milestones are retained. Deep brain stimulation and depression are the main focus. Risk is the disadvantage most commonly mentioned in articles from Canada/USA and Germany, and in reader comments across all countries. German articles almost uniquely, although still minimally, report on ethical issues such as identity and control. Over time, reporting becomes more positive. German media coverage is the most cautious, yet German reader comments are more favorable than those from Canada/USA.

While modern press reports about psychiatric neurosurgery reflect growing optimism, the public is divided. Ongoing studies will further inform the influence of media reporting trends on the values, perceptions, and hopes that people hold toward psychiatric neurosurgery, and the significant ways in which these views may shape policy-making for mental health care.

Crucial Challenges in the Fields of Personality Change, Personal Identity and their Legal Classification

Annabel Joschko

As an expression of human dignity, legal capacity is protected by law and describes the ability to have rights and obligations. The German Civil Code uses a dualistic approach to facilitate legal communication: Section 1 of the German Civil Code awards legal capacity to a person with the completion of birth. Therefore, natural persons - including legally competent persons as laid down in Section 104 of the German Civil Code, but also nonviable or physically or mentally disabled persons - are capable of holding rights. Due to the increasing diversity of companies and organizations, it became necessary to introduce a second legal person to the regulatory framework - the legal entity. One of the most controversially discussed questions regarding the advance of neurodegenerative or psychological illnesses is the classification of a person which has experienced a change of personality due to an illness or treatment. Legally however, the person remains the same, but can rather receive special protection such as custodianship. The analysis of (legal) questions in the field of neuroscience may benefit from findings regarding
the advance of new technologies. Especially the progress in the robotics sector and the increased use of artificial intelligence raises the question, whether or not the dualistic approach is still sufficient to provide a transparent and fair distribution of risks or if it is necessary to introduce a third legal person, the electronic person, to hold certain, very advanced and sophisticated robots accountable for damages.
Taking this into account, future challenges can therefore only be met by a transdisciplinary discourse of scientists, ethicists and medical and legal experts.

Loss of Ste20-like kinase as emergent in human epileptogenic malformations impairs high-order dendrite arborization and inhibitory synapse maintenance

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Common causes for refractory epilepsies comprise developmental malformations of the cortex such as gangliogliomas (GG) and focal cortical dysplasia type IIb (FCDIIb). These frequent focal epileptogenic lesions share the disruption of dendritic architecture in dysplastic neurons as common hallmark. However, the underlying molecular mechanisms have so far remained enigmatic. We found expression levels of the Ste20-like kinase (SLK) to be reduced in GG's and FCDIIb's, implying a possible role of the kinase in the regulation of proper excitation/inhibition balance.
Knockdown of SLK by in utero electroporation of short hairpin RNA in mice resulted in a reduced number of higher-order dendrites and a progressive decline of inhibitory synapses after postnatal day 15. Consequently, inhibition was impaired in electrophysiological measurements of single SLK knockdown (KD) neurons and on the network level as the propensity for PTZ-provoked seizures in mice with local cortical SLK KD was increased. In non-neuronal cells, SLK, which is a serine/threonine kinase, influences many cellular processes by phosphorylating target proteins. To gain first insights into SLK's so far unknown mode of action in neurons, we have performed *in vitro* kinase reactions with different candidate proteins. The results of these assays pointed to the inhibitory postsynaptic scaffold protein gephyrin as a possible substrate of SLK.
Taken together, our data point to loss of SLK as a key mechanism underlying the development of hyperexcitability in epileptogenic focal brain lesions.

Participation of Ste20-like kinase deficient neurons in the abnormal circuitry of focal epileptogenic lesions

Royero, P. Robens, B., Schoch S., Becker A., Beck H.

The most frequent epileptogenic focal lesions are mainly characterized by the presence of dysplastic neurons with the hallmark of disrupted dendrite topology. Preliminary data have shown that knock-down (KD) of the Ste20-like kinase (SLK), a regulator of cytoskeletal dynamics that is down-regulated in cortical malformation biopsies, causes strong reduction of inhibitory synapses and an aggravated seizure phenotype. However, it is still unclear how these neurons are contributing to the generation of increased excitability.
We performed sequential *in vitro* recordings of SLK-KD and neighbouring principal cortical neurons while stimulating the subcortical white matter. The amplitude and kinetics of stimulation-evoked excitatory postsynaptic currents (EPSCs) of dysplastic neurons did not show alterations compared to control neurons. Remarkably, the amplitude of evoked-inhibitory postsynaptic currents (IPSCs) was much lower (78.49%, n=8) in dysplastic compared to control neurons. Next, we addressed whether this inhibitory input impairment lies at the feedforward thalamocortical circuitry by expressing channelrhodopsin-2 (ChR2) channel in thalamocortical nuclei. Light activation of thalamocortical fibers produced much lower EPSC and IPSC amplitudes in SLK-KD neurons when compared to controls. Recording both EPSCs and IPSCs from individual cells, allowed us to compute their excitation-inhibition (E/I) ratio. Our experiments indicated that even though dysplastic neurons may display a reduction of both synaptic excitatory and inhibitory inputs, the net result is a shift of the E/I balance towards excitation. This may contribute to the hyperexcitability seen in aberrant neuronal networks and suggests that dysplastic neurons may be instrumental in the generation of pathological activity patterns.

New Role of MCPH1 in the Energetic Metabolism during Neurodevelopment

Javier Gilabert-Juan, Homa Adle-Biassette, Pierre Gressens, Jeannette Nardelli

MCPH1 (BRIT1/Microcephalin1) is a gene firstly described as one of the causes of genetic microcephaly in humans. Mcph1 disruption in mice results in primary microcephaly mimicking human MCPH1 mutation phenotype, and microphtalmia. The gene encodes, at least, two protein isoforms, the full-length protein (MCPH1-FL) and the short-form protein (MCHPH1-ΔC) that lacks the last 6 exons of the full-length protein, including the two C-terminal BRCT domains. These two isoforms have a different pattern of expression in the brain during development. MCPH1 plays a key role in brain development, DNA damage repair and chromosome condensation. In addition, our recent data support mitochondrial localization for MCPH1 both in murine and human neural progenitors, and a mitochondrial metabolism alteration in the MCPH1 deficiency cells.

To better understand the function of MCPH1 in the mitochondria, we have interrogated mouse and human neuroepitelial cells and human retinoblastoma cells in different conditions of glucose and pyruvate availability. Under low glucose availability, MCPH1 presents a high binding to the 75 KDa Glucose-Regulated Protein (GRP75) and to Voltage-dependent Anion Channels (VDAC), both mitochondrial proteins involved in the response of the cell to the low glucose availability. ii) Glutaminolysis is an energetic supply pathway that proliferating and cancer cells often rely on when low availability of glucose. In this pathway, glutamine is transported into the cells, converted to glutamate and further to alpha-ketoglutarate (α-KG) by glutaminase (GLS) to enable ATP production through the TCA cycle. Mitochondrial isoform of phosphoenolpyruvate carboxykinase (Pck2) is a key enzyme of glutaminolysis route, and we found that KO neuroepitelial mice cells for *Mcph1* do not increase the expression of Pck2 protein under low glucose and low pyruvate conditions, pointing the possible regulation of Pck2 protein by Mcph1. iii) MCPH1 isoforms expression varies when cells are deprived of glucose and of both glucose and pyruvate, suggesting the possible different functions of these two isoforms in cell metabolism. iv) MCPH1 and PCK2 are widely expressed in retinoblastoma and medulloblastoma tumors, designating their implication in a possible mechanism of survival of these tumours.

All these data indicate a potential new role of MCPH1 in mitochondrial energetic metabolism during neurodevelopment or neural tumorgenesis.

Unravelling the pathophysiological mechanisms of LIS1-associated human cortical malformations

Cordón-Barris L., Reiner O., Ladewig J., and Nguyen L

LIS1 is a keystone protein in neuronal development that controls various biological activities, such as cellular transport, proliferation of neuronal progenitors and neuronal migration. Functional disruption of this protein is responsible for Miller Dieker syndrome (MDS), characterized by cortical malformations such as different lissencephalic grade of severity and subcortical band heterotopia. In order to decipher the pathological mechanisms resulting from LIS1 mutation, we engineered dorsal cortical progenitors (DCP) from CRISPR/Cas9 edited human embryonic stem cells (hESC) that express reduced levels of LIS1 protein. This cellular model will be used to uncover the molecular pathways and the correspondent cellular functions dysregulated when LIS1 is not properly expressed in early cortical progenitors. The candidate genes connection to LIS1 will be confirmed in this model by gain of function (GOF) or lose of function (LOF) experiments and screened in the exome of different lissencephalic patients.
This study will bring into light the pathophysiology of lissencephaly with new molecular pathways associated to LIS1 disruption that can be target by drugs to prevent, rescue or ameliorate the prognosis of this disease.

LIS1 takes the RISC

Aditya Kshirsagar, Tsviya Olender, Orly Reiner

LIS1 (also known as PAFAH1B1) has been associated with Lissencephaly; a condition wherein the cerebral cortex of the patients with the mutation assumes a smooth shape. In mice, the Lis1 knockout is early embryonic lethal around E-3.5. The critical analysis of staining in wild type blastocyst affirms that LIS1 localizes predominantly in cortical ICM cells. We performed an integrated high throughput analysis of RNA and proteins in the embryonic stem cells and found that LIS1 interacts with Argonaute proteins (RISC-RNA induced silencing complex) and several ES cell known epigenetic regulators controlling the gene and miRNA expression in ES cells.

Capturing different disease severities of LIS1-lissencephaly in iPSC-derived cerebral organoids

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The development of the human cortex requires a precise choreography of progenitor proliferation, neurogenesis and neuronal migration, which can be disrupted in malformations of cortical development (MCDs). In the past, most studies on MCD were performed in mouse models. Critical structural differences between human and mice might, however, necessitate the use of additional model systems. In this context, pluripotent stem cell (PSC)-derived three-dimensional (3D) cerebral organoids, which faithfully recapitulate certain aspect of human brain development *in vitro*, have emerged as an attractive alternative. Here we used forebrain specific cerebral organoids derived from human induced (i)PSCs to address the variable phenotypic severities of *LIS*1-lissencephaly, which is characterized by a smooth brain and a disorganized cortex. The *LIS*1-protein is one component of an intracellular multiprotein complex essential for the regulation of cytoplasmic dynein, centrosomal protein localization and microtubule dynamics. When applying our cortical organoid model to iPSCs derived from patients exhibiting different severity grades within the *LIS*1-lissencephaly spectrum, we found disease-related phenotypes that capture the variable phenotypic severities. In particular, we observed that organoids from individuals with mild or severe disease show either mild or severe alterations in the organization of vRGCs' microtubule networks, in disruption of the architecture of the cortical niche and in altered expression of cell adhesion molecules. These data indicate that iPSC based 3D cortical organoids represent a sensitive tool which allows to recapitulate variable disease severities, and can thus contribute to an advanced understanding of developmental mechanisms and disease-related changes caused by the dysfunction of single genes.

Linking positional identity to cell cycle dynamics: COUP-TFI controls neural stem cell proliferation in the caudal cortex

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During development, neural progenitor cells (NPCs) build the cerebral cortex by means of a delicate balance between neurogenesis and progenitor maintenance. However, the molecular mechanisms allowing the orchestrated production of the correct type of neurons, in the right place, at the right time, are still not well understood.

The transcriptional regulator COUP-TFI, expressed along the cortex following a high-caudal to low-rostral gradient in progenitors and postmitotic neurons, plays several key roles during late corticogenesis and areal organization. Here we decided to investigate its early potential function in NPCs, focusing on the most caudal area of the neocortex, where COUP-TFI is strongly expressed.

Exploiting a COUP-TFI knock-out mouse model, we show that this gene controls the balance between self-renewal and neurogenesis. Particularly, the cell cycle is strongly accelerated in mutants, and the symmetric proliferative cell divisions increase at the expense of asymmetric ones, resulting in the early expansion of the NPC pool. The early tangential expansion of the caudal cortex is followed by a radial two-fold increase in neuronal production, leading to the formation of an aberrantly thick cortical plate in the most caudal region of the neocortex, where the visual and auditory areas are generated.

Overall, our data demonstrate that COUP-TFI operates a fine-tuned control of NPC physiology, linking the rostro-caudal positional identity to the local progenitor activity, ultimately orchestrating the correct morphology of distinct protoareas during development.

Role of cux genes in retina development

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Cux1 and *Cux2* are members of the *Cut* family of transcription factors, which contribute to different developmental events in the nervous system. Cux2 controls the proliferation of neuronal progenitors of cortical layers II-III and IV, as well as those of the olfactory epithelium and spinal cord. Cux1 instead regulates callosal projection formation. Both genes have been involved in neuronal differentiation, including the control of dendritic branching and number of spines in neurons of the upper cortical layers. Both transcription factors have been associated with brain disorders of developmental origin, such as depression, bipolar disorder and autism spectrum disorders. Whether *Cux* genes have any role in retina development is however still unexplored. Here we have begun to address this question by determining the precise expression pattern dynamics of both genes during eye formation and by analyzing their loss of function. Our initial results show that *Cux1* is expressed in the retinal layer at optic cup stages and both *Cux1* and *Cux2* localize to a subpopulation of retinal ganglion cells (RGCs) and to cells of the neuroblastic layer. Analysis of the retinal phenotype of $Cux1^{-/-}$ and $Cux2^{-/-}$ mice reveal similar retinal defects, characterized by alterations in the organization and number of the RGCs. Furthermore, the inner plexiform layer (IPL) is reduced in thickness and the amacrine cell layer is affected, suggesting the possibility that in the retina Cux genes regulate both the number of neurons and the growth of their processes, similarly as in the cortex. Ongoing studies will elucidate these possibilities.

The Sox2 transcription factor is required for the development of the visual system in mouse

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Neurodevelopmental visual disorders can originate from genetic defects that affect the embryonic development of the various components of the "visual system": the eyes, the dorsolateral geniculate nucleus (dLGN) in the thalamus and the visual cortex. The Sox2 gene encodes a transcription factor that is expressed in the eyes, the dLGN and the developing cortex and is mutated in patients with severe vision and brain defects.

To understand the role of Sox2 in the development of the visual system we generated cortical and thalamic Sox2 conditional knock-outs (cKO) in mouse. In the Sox2 cortical cKO (Sox2 ablation starts at E10.5) the primary visual area (V1) is slightly reduced in size. On the other hand, in the thalamic cKO (Sox2 ablation starts at E14.5) the dLGN is greatly reduced in size. Projections from the dLGN to the V1 are almost absent in Sox2 thalamic mutants and projections from the eyes to the dLGN are disorganized suggesting that the expression of axon guidance molecules could be affected in the mutant dLGN. Sox2 thalamic mutants have abnormalities that closely mirror those found in COUP-TF1 mutants. We found that Sox2 and CoupTf1 are co-expressed in neurons in the dLGN and we are searching for genes that could be co-regulated by Sox2 and COUP-TF1 and could be affected in our Sox2 mutants.

A role for Sox2 in eye development had been previously described and we have now identified its importance for the development of other components of the visual system: the thalamus and cortex.

Short-term deprivation of the amblyopic eye, combined with physical exercise, promotes long-term visual recovery in adult anisometropic patients

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We have recently shown that the adult visual cortex retains a high degree of neuroplasticity: short-term monocular deprivation unexpectedly boosts the deprived eye during binocular rivalry (Lunghi et al 2011), and this effect is further enhanced by physical activity (Lunghi & Sale, 2015). As boosting neuroplasticity is fundamental for the treatment of amblyopia, we attempted a counterintuitive experiment where we deprived the amblyopic instead of the dominant eye in adult patients, combining monocular patching and physical activity. In ten anisometropic patients (mean age 31.5±5 years, mean amblyopic eye acuity 0.39±0.23 LogMar), with no associated strabismus, we patched the amblyopic eye for two hours over three consecutive days, then once per week over the next three weeks. During the patching period patients watched a movie while intermittently cycling on an exercise bike. Before and after each patching session we measured binocular rivalry (orthogonal gratings, size 2°, SF: 2 cpd), visual acuity (LogMar charts) and stereoacuity (TNO test).The perceptual dominance of the patched eye increased after deprivation similar to the effect found in normal subjects. Visual acuity improved in all patients (average improvement: 0.15 LogMar, $t(9)=8.04$, $p<0.001$), and 6/10 patients also recovered stereopsis. Strikingly, the improvement in both V.A. and stereopsis was preserved for at least 3 months after testing. These results show that amblyopic eye vision can be improved by transiently depriving the weak rather than the strong eye, probably by activating homeostatic plasticity. Physical exercise may be crucial for the recovery by potentiating the plastic potential of the visual cortex.

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Short-term monocular deprivation could be driven by an interocular contrast gain control mechanism

Alexandre Reynaud, Jiawei Zhou and Robert F. Hess

Short-term monocular deprivation induces a shift in the interocular balance in favor of the previously deprived eye. In order to test if this effect could be driven by an interocular contrast gain control mechanism, we designed a protocol where participants were viewing filtered dichoptic movies during 2 hours. The dominant eye was fully deprived, seeing mean gray, and the other one was stimulated at different contrasts 12%, 24%, 50% or 100% in four different sessions. Each eye's contribution was measured with a phase combination task before and after the viewing period. Our results show that the shift induced in the interocular balance depends on the interocular contrast difference during the viewing period. The bigger the contrast difference, the bigger the shift. These observations indeed suggest that these effects are driven by an interocular contrast gain control mechanism.

Virtual-Reality Software for the Diagnosis and Treatment of Amblyopia and Strabismus

Johann Schneider and Jochen Triesch

One of the major causes for impaired vision in young children is amblyopia, a neu- rodevelopmental disorder of the visual system where vision is reduced in one eye that otherwise appears normal. In many cases this reduction arises from a suppression of signals from the a_ected eye by the una_ected, so called \fellow" eye. Often ambly- opia results from another disorder - strabismus - which is a misalignment of the eyes. Both diseases can strongly impair binocular visual functions such as stereo vision and binocular fusion. We present a software for the diagnosis and treatment of these disorders using a mod- ern virtual-reality (VR) head-mounted-display (HMD) with an integrated eye-tracking system. The software consists of several tests which measure the alignment of the eyes and the suppression of the amblyopic eye by the fellow eye. In order to facilitate proper binocular vision some results from the measurements are used to provide corrections to the images displayed in the HMD. For treatment we have developed an arcade-like VR videogame which targets stereo vision and binocular fusion. Successful gameplay leads to a stepwise reduction of the applied corrections with the goal of eventually driving the system towards normal vision. A rst study with the software is currently being prepared.

Digital or analogue? First assessment of newly developed digital stereotests

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Background: The TNO (Laméris Ootech, NL) is a standard clinical test for measuring stereo vision. Recently new stereotests for modern display technologies were developed by the McGill Vision Research Unit, Montreal and implemented at the Goethe University Child Vision Research Unit, Frankfurt (both Neuro-DREAM project partners). Our questions of interest were: How reliable are test-retest measurements with the new digital tests? How do the digital and the clinical tests correlate?
Methods: The digital tests were presented either on an iPod (red-green anaglyph glasses) or a 3D monitor (shutter glasses) and the TNO on printed test plates (red-green glasses). All three use a random-dot based circular stimulus with a gap at one of the four cardinal directions, where participants need to identify the correct gap position. We tested 25 normal-sighted participants and 7 amblyopes (age range 4-59 years) with both the TNO, and the iPod and 3D monitor stereotests.
Results: Repeated measurements were significantly correlated for both the iPod (ICR= 0.95) and the 3D monitor (ICR= 0.96) stereo test. Comparisons showed moderate agreement and somewhat finer stereo acuity on the TNO than on the digital tests.
Conclusion: Test-retest measures showed a high correlation and point to reliable measures for the digital tests. Differences between the digital tests and the TNO could be explained by differences in threshold assessment or the implemented "forced-choice" paradigm. For future research, more participants (especially amblyopes) will be included to validate the results and changes will be made to the digital stereo tests so that threshold calculation is refined.

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MCI-patients' and caregivers' expectations towards risk prediction of ad: preliminary findings from the PREDADQOL interview study

Carolin Schwegler, Ayda Rostamzadeh, Frank Jessen, Mercè Boada, Christiane Woopen

Today, a growing number of individuals with mild cognitive impairment (MCI) accept the offer for biomarker-based prediction of Alzheimer's Disease (AD). However, the expectations and attitudes of patients and their caregivers are widely unknown. The aim of this qualitative analysis is to examine these specific attitudes and expectations towards risk prediction and the future quality of life.

Within this first approach, individual interviews are conducted with ten participants. The examination is part of a longitudinal qualitative and quantitative study (PreDADQoL), which aims to develop standardized guidance for information, counselling, and support with regard to risk prediction of AD. After information and counselling by a trained clinician, semi-structured interviews are conducted, in which the interviewer asks for specific situational experiences, expectations towards the predictive diagnostics, and ideas about the future. During the narrative parts of the interview and through describing situational experiences, participants show their attitude and expectations towards the offered diagnosis in multifaceted ways.

The analysis points out that most participants want to attain more certainty about their future state of health and want to assess their syndromes with the best existing medical technologies. Furthermore, the majority is primarily interested in the understanding of their current and future health status and do not reflect the consequences of predictive knowledge.

Regarding the major psychosocial and ethical impact of predictive knowledge, information and counselling of patients with MCI should take into account their attitudes and expectations. Further research is needed to develop a standardized guidance in form of an adequate counselling protocol.