

Poster 1

Title: Age-related differences in problem-solving and learning by insight

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Abstract:

Problem-solving and episodic memory processes are important for daily life, but depend on complex cognitive functions that decline with age. Problem solving by insight represents a special associative process of problem solving, in which the emotional component of the Aha! experience is of great importance. This Aha! experience is characterized by a positive feeling upon the sudden comprehension of the solution. Regarding long-term memory formation, problem solving by insight has been linked to a network independent of the hippocampus. Because this structure shows structural changes early on in older adults, problem solving by insight may represent a cognitive resource for learning at older age.

Using the Compound Remote Associate Task (CRAT), this study investigated differences between young (19 - 28 years) and older subjects (60 - 79 years) in problem solving and learning by insight. On the first day, during an incidental learning task, the 61 participants judged the plausibility of presented (pseudo-)solutions for valid and nonsense CRA items. The day after, direct memory was tested by a retrieval task and indirect memory was assessed by solution rates and reaction times.

Older subjects showed advantages in the area of plausibility judgement of the puzzles and a verbal intelligence screening. A higher score in the latter was correlated with solution frequency of known puzzles in older participants. Young subjects answered faster and more correctly and were better able to classify the familiarity of the puzzles. With respect to the relative frequency of solving new word puzzles, both age groups showed equal performance. This suggests an associative problem-solving process in which older people are not at a disadvantage due to aging processes. Young participant showed better memory performance, but older participants benefited more from problem solving by insight than without insight regarding later recognition memory of the items. Therefore, problem solving by insight might represent a way to support memory performance in old age.

Another focus of the study was to assess potential age-related differences in the facets of the subjective Aha! experience and problem-solving strategies. None of the four criteria for Aha! (positive feeling, suddenness, conviction of correctness, surprise) was found to be of key importance in both age groups. However, both groups reported Aha! experiences more often when the solution was actually correct than when the answer was incorrect, which is in line with previous findings for young adults. The young participants more often attempted to use cognitive solution strategies, while the older participants were more likely to use associative approaches. Associative problem solving led to higher solution rates than cognitive strategies in young adults in previous studies and may represent another potential advantage for cognitive performance in older adults.

Poster 2

Title: CSF and PET biomarkers for noradrenergic dysfunction in neurodegenerative disease: a systematic review and meta-analysis

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Abstract:

Introduction: The noradrenergic system shows pathological modifications in aging and neurodegenerative diseases and is thought to be affected in the early stages of both Alzheimer and Parkinson's diseases.

Methods and Findings: We conducted a meta-analysis of noradrenergic differences in Alzheimer's disease type dementia (ADD) and Parkinson's disease (PD) using CSF and PET biomarkers. CSF noradrenaline (NA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) as well as NA transporter availability (PET MeNER) levels in controls, ADD and PD patients was summarized from 26 articles (841 participants in total) using a random-effects model metaanalysis.

Results: Compared with controls, PD patients showed significant reductions in CSF NA and MHPG, and PET MeNER binding in the hypothalamus. In ADD, MHPG levels were increased compared with controls. Age correlated with CSF MHPG levels in ADD, but not in PD.

Conclusions: Noradrenergic dysfunction in neurodegenerative diseases can be detected using CSF or PET measures and may be more pronounced in PD compared to ADD.

Poster 3

Title: Neddylation-dependent protein degradation is a nexus between synaptic insulin resistance, neuroinflammation and Alzheimer's disease

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Abstract:

The Metabolic syndrome (MetS) is a consequence of modern lifestyle; it is characterized by obesity, insulin resistance, high glucose levels, and hypertension. Many studies have shown that MetS is correlated with synaptic IR, diabetes and a 10-fold higher risk to develop late-onset Alzheimer's disease (AD). Accordingly, synaptic IR in the hippocampus by itself negatively affects cognition inducing impairments in learning and memory.

In this study, we hypothesize that synaptic IR, with neuroinflammation and amyloid β load, interact inducing synaptic dysfunction and all those factors converge on neddylation of cullins and the ubiquitination of the Insulin receptor substrate 1 (IRS1) in the hippocampus.

Neddylation is a post-translation modification that refers to the conjugation of Nedd8 to a lysine residue of a target protein. Until now only a few neddylation targets are identified including Cullins proteins, which are the core component of Cullins-RING E3 (CRLs) ubiquitin ligase complex. The major role of Nedd8 is to activate CRLs but little is known about its role in neurons and other substrates of this process.

In our work, we use primary neurons to induce synaptic insulin resistance as well as a mouse model of high-risk aging that includes amyloid load, neuroinflammation, and diet-induced obesity to test hypotheses on the mechanism behind this interaction in promoting the onset of AD.

Moreover, with the usage of specific tools which have been developed in our laboratory, we want to shed a light on the many questions that remain open regarding the role of Neddylation at the synaptic level. We report that neddylation and subsequent activation of cullin-RING ligase complexes induce synaptic insulin resistance by ubiquitylation and degradation of the insulin-receptor substrate IRS1 that organizes synaptic insulin signaling. Accordingly, inhibition of neddylation preserves synaptic insulin signaling and seems to play a role in restoring memory deficits in mice with a high amyloid load, which were fed with a 'western diet'.

Due to the lack of knowledge regarding the role that neddylation might play in the aging brain, we will investigate:

- the regulation of neddylation at the synapse and the localization of the main component of the pathway at the synaptic level;
- the neddylated proteins in the brains using an animal model for a population of high-risk aging with increased amyloid load, the TBA2.1.

Poster 4

Title: Impact of immunosenescence on *T. gondii* infection-induced neuroinflammation

Authors and Affiliations:

Tabea Linde, Dr. Johannes Steffen, Prof. Dr. Ildiko Dunay

Abstract:

Healthy aging is accompanied by the progressive remodelling of the immune system and its decline in efficacy, referred to as “immunosenescence”, which affects both innate and acquired immune responses. Immunosenescence greatly contributes to increased susceptibility to infections in the elderly. Besides aging, infections and inflammation are similarly able to induce changes in cognitive function, neuronal connectivity and cellular functionality. *Toxoplasma gondii* (*T. gondii*), an intracellular parasite whose seroprevalence markedly increases with age, is able to cross the blood-brain barrier and persists lifelong in tissue cysts, thus evoking sustained basal neuroinflammation.

To address the effects of immunosenescence over the course of the infection-induced neuroinflammation, we characterised phenotype and activation status of immune cells in the CNS and periphery of young and aged C57BL/6J mice upon *T. gondii* infection. In aged animals, recruitment of myeloid cells to the CNS was impaired. Moreover, total cell numbers of brain resident cells were also reduced in aged animals. To study changes in neuronal connectivity, we first established an *in vitro* phagocytosis assay using bone marrow-derived macrophages and labelled synaptosomes to mimic synaptic pruning. Phagocytic capacities receded with infection status and further with age.

Collectively, these findings provide evidence that immunosenescence in the CNS results in reduced microglial numbers, limited recruitment of peripheral immune cells as well as functional impairments. The extent to which each immune cell subset is involved and may further contribute to synaptic alterations is currently being investigated.

Poster 5

Title: Impact of DNA methylation of the CALN1 gene on very late-onset schizophrenia

Authors and Affiliations:

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Abstract:

Schizophrenia is a complex debilitating disorder that affects approximately 1% of the world population with an onset in most cases in early-adulthood. There are strong evidences for a genetic component of the disease. Schizophrenic patients show a wide range of symptoms, positive ones that include delusions, hallucinations, thought disorders, negative ones that include social withdrawal, poverty of speech as well as cognitive impairments. The pre-frontal cortex has been shown to be highly relevant for the pathology, especially for negative symptoms and cognitive impairments. Increasing evidence indicates a significant role of muscarinic signaling in Schizophrenia. Muscarinic signaling has been shown to be impaired in human patients as well as in a schizophrenic mouse model. Interestingly, for more than 10% of all cases of Schizophrenia, the first symptoms appear after 40 years of age. Yet, it is still unclear how a pathology considered to be developmental can emerge in this later stage of life.

In this study we investigate a risk gene for Schizophrenia, the calcium-binding protein Calneuron-1. In our work we showed that Calneuron-1 expression is elevated at both the mRNA and protein levels in the medial pre-frontal cortex of schizophrenic patients. We also showed that Calneuron-1 interacts directly with the M1R and negatively regulates muscarinic signaling. Furthermore, Calneuron-1 overexpression in the mice PFC is sufficient to reduce the expression of muscarinic long-term depression, a form of long-term depression relevant for schizophrenia.

We found Calneuron-1 to be much more abundant in 2-year-old mice compared to 3-month-old mice at both mRNA and protein levels. In future work we will assess if elevated Calneuron-1 expression in the pre-frontal cortex of mice is a risk factor to induce schizophrenic-like behaviors in an age-dependent manner.

Poster 6

Title: Anxiety behavior in young and old brevican and neurocan double knock-out mice kept in lifelong enriched environment

Authors and Affiliations:

Jana Schulze, Dr. Anil Annamneedi, Prof. Dr. Oliver Stork, Prof. Dr. Eckart Gundelfinger, Prof. Dr. Constanze Seidenbecher

Abstract:

Enriched environment (EE) is well-known to positively affect cognitive abilities and anxiety even when applied short term only. Studies show that EE ameliorates effects from neurocognitive diseases and ageing. Enrichment promotes neurogenesis, synaptic plasticity and restructuring of the extracellular matrix (ECM), effectively counteracting effects of neuronal ageing. The ECM shows age-related changes including an increase of the proteoglycans brevican and neurocan and the link protein HAPLN1. These changes were shown to be associated with cognitive decline in old mice. Neurocan is also linked to manic behavior, as shown by a behavioral study in mice and genome wide association studies in humans, and thus might be involved in changes of anxiety during ageing and enriched rearing. Here we investigate the role of proteoglycans neurocan and brevican in anxiety-like behavior during ageing and if EE has an anxiolytic effect in mice deficient for the two proteoglycans.

Double knockout and wild type mice were reared in EE including a running wheel for their entire life and compared to standard-reared animals at 3-4 months or 17-18 months of age. Anxiety levels were analyzed in an open field arena and brains were taken for biochemical analysis after behavioral testing.

An anxiolytic effect of long-term EE was observed in young wild type mice, while double knockouts did not show decreased anxiety levels after enriched rearing. Neither group of old animals showed an anxiolytic effect of enrichment. Immunoblot analysis confirmed the expected increase of HAPLN1 in old animals, regardless of genotype and rearing. Apart from that, the double knockout of brevican and neurocan can be associated with an increase of HAPLN1 in young mice.

Taken together our data indicates that neurocan and brevican are essential for the anxiolytic effect of EE in young adult mice. In old animals this effect might be lacking because of habituation to the lifelong enrichment.

Poster 7

Title: Glycosylation in the Context of Disturbed Blood-Brain Barrier and Microglial Function in Alzheimer's Disease

Authors and Affiliations:

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Abstract:

Alzheimer's disease (AD) is the leading cause of dementia. The two histopathological markers of AD are amyloid plaques composed of the amyloid- β (A β) peptide, and neurofibrillary tangles of aggregated, abnormally hyper-phosphorylated tau protein. The majority of AD cases are late-onset AD (LOAD), after the age of 65, where a clear cause is still unknown. However, there are different multifactorial contributors including genetics, which can increase risk for the disease. Apolipoprotein E (APOE^{4/4}) genotype is already an established risk factor for LOAD as shown by genome-wide association studies. Genetic factors such as rare variants of TREM2 (triggering receptor expressed on myeloid cells-2) and CD33 strongly increase the risk of developing AD, confirming the role of microglia in AD pathogenesis. Rare variants in the ABCA7 (ATP-binding cassette, subfamily A, member 7) gene recommend the analysis of disturbed blood-brain barrier function in AD patients. Therefore, we developed and characterised a blood-brain barrier model and microglia-like cell model from patient-derived induced pluripotent stem cells harbouring the risk genes for AD. These established models are being used to study the pathology of AD and the contribution of risk variants to the disease.

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Poster 8

Title: Regulation of NPYergic neurotransmission and plasticity in an estrous cycle dependent manner in the dentate gyrus

Authors and Affiliations:

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Abstract:

Impact of sex hormones and gender on memory formation, plasticity and excitability has been extensively studied. Apart from its direct effects on neuronal function and plasticity, the sex hormone estrogen interacts with other neuromodulatory systems and alter the use of cognitive resources via regulation of circuit plasticity and excitability. One key neuromodulatory system that is substantially affected by estrogen is NPYergic system. Interestingly, NPYergic regulation of excitability in the dorsal dentate gyrus (dDG) appears to be a key mechanism that regulates the salience of contextual fear memory in male mice.

In the current study, we aimed to study the NPYergic regulation of dDG excitability and plasticity in female mice with intact estrous cycle. We performed extracellular field potential recordings from medial perforant path (MPP)-to-dDG synapse in hippocampal slice preparation using a stimulation protocol that allow us to study plasticity under intact inhibitory neurotransmission. Our data show that the ability to induce long-term potentiation (LTP) in the MPP-to-dDG synapse is dependent on the cycle stage. Next, we observed that increased baseline transmission by blocking the Y1 receptor via BIBP3326 is only observed in the high estrous state females, indicating a potential increase in endogenous NPYergic neurotransmission in high estrous stage when endogenous estrogen levels are high. Of note, in male mice, the increase in NPYergic transmission is mediated by acetylcholine via M1-receptors.

This data demonstrate that the Y1-receptor mediated DG inhibition differs along the estrous cycle and might be mediated by combination of an indirect and direct activation of NPYergic interneurons.

Poster 9

Title: Modelling fragile X-associated neuropsychiatric disorders in an inducible mouse model: Increased anxiety, aberrant gamma oscillations and reduced parvalbumin-positive interneurons

Authors and Affiliations:

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Abstract:

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder that affects the carriers of fragile X premutation with 55 to 200 CGG repeats. Motor dysfunction is the hallmark of FXTAS. However, the neuropsychiatric disorders including anxiety and depression are the most common problems affecting the ~50% of premutation carriers. These neuropsychiatric disorders coincide and even precede the motor dysfunction. Despite these clinical observations, neurobiological mechanisms underlying the fragile X-associated neuropsychiatric disorders (FXAND) have not been addressed in a FXTAS model.

Here, we aimed to study the anxiety phenotype without any interference from motor deficits using an early induction schedule starting from embryonic development. No motor dysfunction was detected in this mouse model although an anxiety-like phenotype was already present. We hypothesized that physiological changes in the ventral hippocampus and amygdala might determine the development of anxiety phenotype. Electrophysiological analysis reveals an enhanced excitability in the lateral amygdala together with increased gamma oscillations and augmented CA3-CA1 gamma correlation in the ventral hippocampus. These observations were linked to impaired short-term and long-term plasticity in the CA3 recurrent network. These pathological alterations together with the reduced number of positive parvalbumin interneurons in the ventral hippocampus and the increased inclusion load in the lateral amygdala and ventral hippocampus could be normalized upon cessation of DOX administration.

This study suggests that these neurophysiological features can be interpreted as a marker for anxiety disorders in the fragile X premutation carriers.

Poster 10

Title: Astrocyte-Neuron metabolic association from the perspective of synaptic aging: L-/D-Serine pathway and investigating pharmacological rejuvenation of synapses

Authors and Affiliations:

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Abstract:

The astrocyte-neuron interaction is crucial in terms of metabolic exchange, where each cell type has a significant effect on the function of the other, but its contribution to pathological conditions and aging is poorly understood. The L-Serine biosynthetic pathway is one such important metabolic link between neurons and astrocytes given that L-Serine – solely produced by astrocytes in the nervous system – is also an important metabolite in the production of, among other things, the two main N-methyl-D-aspartate-receptor (NMDAR) agonists D-Serine and Glycine. Using cortical tissue, it was possible to see the up- or down-regulation of a select group of proteins mainly involved in the L-/D-Serine metabolic pathway as well as in NMDAR signalling across three different ages: 2- month, 6- month and 24-month-old C57BL/6 mice. Concurrently, measuring L-/D-Serine concentrations in cortical tissue showed a decrease in both L- and D-Serine during aging, suggesting crucial changes are occurring in this pathway that may influence synaptic aging. In addition to probing the protein expression and metabolic changes that occur due to aging, several previous studies have also looked at the possibility of alleviating the detrimental consequences of cognitive aging with varied results across different model systems. Metformin, a drug primarily prescribed against type 2 diabetes has been shown to increase lifespan in some organisms. How metformin might induce proteomic, metabolic, or structural changes specifically in astrocytes and how Metformin might influence the L-/D-serine metabolic pathway and NMDA receptor signalling at the aging synapse will be investigated using a previously established mouse model that allows identification and analysis of changes in protein translation by amino acid tagging.

Poster 11

Title: Investigating error-improved associative memory representations of cue and target stimuli using cross-task MVPA in fMRI

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Abstract:

Introduction: The recognition of missing or wrong memories can upregulate selective attention to improve performance in the next learning situation. However, the brain mechanisms underlying the enhancement of cue and target representations during memory encoding are not well understood.

Methods: For this purpose, we developed a cognitive paradigm addressing error monitoring processes during associative memory formation with unknown faces as cue and gabor patch orientations as target stimuli. On a separate 1-back task, (1) one support vector machine was trained to distinguish between faces and houses, and (2) one was trained to differentiate between gabor patch orientations. These two models were used to predict cue and target representations during time of encoding in the memory task, and then investigated regarding their hemodynamic topography.

Results: Preliminary results indicate that the decision of the algorithm to predict cue (face) representations is related to clusters in regions among dorsolateral prefrontal cortex, posterior medial frontal cortex, amygdala and hippocampus – while the algorithm was only trained on predefined face-selective voxels within fusiform gyrus and lateral occipital cortex. These ongoing analyses will further focus on addressing the topography of target (gabor patch orientation) representations, and the general relationship of these representations with the success of memory encoding.

Interpretation: In general, task-based fMRI studies have rarely predicted cognitive states across different tasks. Such analyses may, however, help to elucidate more robust models of endogenous brain states underlying enhanced formation of memory representations.

Keywords: performance monitoring, cognitive control, representational similarity analysis, generalizability

Poster 12

Title: Literature-based probabilistic regions of interest improve the classification of Alzheimer's Disease and Mild Cognitive Impairment based on grey-matter density maps

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Abstract:

Machine learning applications for classification of a disease state have been gaining increasing popularity over the last couple of years. Classification of neuroimaging data from patients with Alzheimer's disease (AD) is often performed with whole-brain or hippocampal grey-matter density (GMD) maps, as well as brain atlas based parcellation techniques. In this work, we propose the use of literature-based probabilistic regions of interest (pROIs) to improve classification of structural MRI. For this purpose, twenty atlas-independent pROIs were computed from a collection of voxel-based morphometry studies on AD. The pROIs were used as feature sets to train a classifier on two data sets, which consisted of GMD maps obtained from participants with AD and Mild Cognitive Impairment. The performance of the proposed pROI classifier was compared with three previously established classifiers: whole-brain classification, hippocampus-based classification and classification using anatomical ROIs. With regard to balanced accuracy, class accuracy and the area under the curve, the pROI classifier outperformed all other classifiers for both data sets. This approach shows a high potential for machine-learning-assisted diagnosis of AD. Moreover, this method is a promising contender for classifying earlier Alzheimer's risk states and predicting future conversion to AD because progression of grey matter atrophy due to AD is highly probable to occur preferentially within the pROIs during earlier stages of the disease, albeit at a smaller scale.

Poster 13

Title: Dysbalanced protein homeostasis as a hallmark and intervention target for aging cells

Authors and Affiliations:

Natalia Waal, Peter Landgraf and Daniela C. Dieterich

Abstract:

The aim of this project is to describe the protein homeostasis (proteostasis) in aged cortical cultures and aged mice brains compared to young ones. Aging itself is a multidimensional process that is characterized by accumulation of damage due to functional decline [C. López-Otín et al., 2013]. This time-dependent decline manifests among other things in dysfunction of the proteostasis [R. C. Taylor and A. Dillin, 2011]. A potential intervention target are naturally occurring polyamines such as putrescine, spermidine and spermine. Polyamines are due to their properties involved in fundamental processes such as cell growth, differentiation and proliferation. The application of exogenous spermidine extends lifespan, improves neuronal and cognitive functions and shows neuroprotective functions in various model organisms [F. Madeo et al., 2018]. It could be shown that the *de novo* protein synthesis for neuronal cells in culture declines with age when comparing DIV20 to DIV80 neurons. Spermidine is involved in the post-translational modification of the eukaryotic translation initiation factor 5A (eIF5A). The modification into eIF5A is essential for the promotion of translation and represents an important key link between polyamines and cell growth regulations. Therefore, constructs were cloned to induce and describe a knock-down and over expression effect of enzymes which are involved in the modification of eIF5A and spermidine synthase. Furthermore, it could be shown in brain homogenates of 18-month-old mice that spermidine has an effect on phosphorylated eukaryotic translation initiation factor 2A (eIF2A). EIF2A acts by directing the binding of Met-tRNA_i to 40S ribosomal subunits. Its phosphorylation is part of an integrated stress response in ribosomal stalling [Yan & Zaher, 2021]. To analyze the ribosome profile of cell culture and brain samples the method of polysome profiling was established. This gives the possibility to describe the translation status in different age groups. Subsequently, the ribosomal profile is compared by exogenous addition of spermidine. Moreover, in an exploratory study the transcriptome will be analyzed via RNAseq. The protein expression will be examined under physiological conditions as well as under the modulation by spermidine. Thus, it is aimed to identify signal cascades that are involved in the aging process.

