both produce and uptake beta-amyloid. AD astrocytes secrete significantly higher amounts of the 1-42 form and show an elevated 1-42/1-40 ratio as compared to controls, but respond well to treatment with gamma-secretase inhibitor DAPT. **Conclusions:** Our data show that pathological findings commonly seen in AD patients are recapitulated in the iPSC-derived astrocytes. Thus, these cells offer a valuable tool for studying the disease mechanisms and for drug screening and testing novel therapeutic approaches in a cell-type specific manner.

**P3-171 ACUTE, TRANSIENT INCREASE IN SECRETION OF NEURODEGENERATION BIOMARKERS AFTER IRRADIATION OF HUMAN CORtical NEURONS**

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**Background:** Radiotherapy is a commonly used therapy for brain tumor control or prevention, but many patients display persistent and deteriorating cognitive function following treatment. Children receiving cranial radiation therapy are especially affected and currently little is known about the underlying mechanisms. The chronic symptoms often become apparent after approximately one year, but could nonetheless be a result of acute cell damage upon irradiation. More understanding of the mechanisms behind radiation-induced acute neuronal damage is needed in order to predict and prevent severe side effects after radiotherapy. We have previously reported a prolonged but transient increase in cerebrospinal fluid levels of the neuronal proteins tau and neurofilament light (NFL) from patients undergoing prophyllactic cranial radiotherapy, suggesting a potential for these proteins as biomarkers also for the brain damage observed after irradiation. Here, we use a human cortical cell model to investigate the neuronal release of these proteins in response to ionizing radiation in more detail. **Methods:** Human iPSC-derived cortical neurons were irradiated with a single dose of 0.5-, 1.5- or 4.5-Gy ionizing radiation, respectively, at two time points during differentiation and followed during a four-week period post-irradiation. Cells and media were collected at different time points after irradiation and compared to non-irradiated control. Secreted tau and NFL were measured in the media using electrochemiluminescence assays. Gene expression was monitored with qPCR. **Results:** Both tau and NFL secretion to the cell media increased dose-dependently during the first four days following irradiation. The secretion peaked after four days and returned to basal or slightly elevated levels within one-two weeks. Despite this, signs of astrocyte activation and altered cell division patterns were still observed one month after irradiation. Effects were more accentuated in cells irradiated at an earlier differentiation stage. **Conclusions:** Ionizing irradiation of cortical neuronal cultures induced a transient increase in tau and NFL secretion. The observed effects were more accentuated in less differentiated neurons, suggesting that developing neurons are especially sensitive to radiation-induced injury. These results correlate well with the clinical situation, showing the potential for the cell model in further investigation of neuronal responses to radiation-induced cell damage.

**P3-172 WITHDRAWN**

**P3-173 ZCCHC17 IMPAIRMENT IS A SIGNIFICANT DRIVER OF NEURONAL DYSFUNCTION IN ALZHEIMER’S DISEASE**

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**Background:** Our laboratory is using bioinformatic tools to investigate potential master regulators of gene expression in cortical neurons that are disrupted in Alzheimer’s disease (AD). This analysis has resulted in the identification of a protein (called ZCCHC17) which is ranked highly in our analysis in two important ways: 1) As a potential master regulator of gene expression generally, and 2) As a potential master regulator of synaptic genes specifically. Our analysis predicts that ZCCHC17 has impaired activity in AD, and that this impairment may partially explain dysregulation of synaptic gene expression in AD. Our goal is to experimentally test these predictions and investigate the mechanism of how this occurs. **Methods:** We have examined ZCCHC17 protein levels in human AD brain tissue and investigated its physiologic role in rodent cortical cultures and (more recently) in human iPSC (induced pluripotent stem cell) neurons. **Results:** We have determined that ZCCHC17 protein (I) Is localized to neuronal nuclei and nucleoli in the CNS, (II) Is decreased in Alzheimer’s disease brain tissue, (III) Directly or Indirectly regulates gene expression of 60% of its predicted synaptic targets in rodent cortical cultures, and (IV) ZCCHC17 knock-down causes aberrations in both the potassium current and in calcium-mediated activity. Current work in our laboratory is focused on better understanding the normal physiologic role of ZCCHC17 and how this contributes to our understanding of neurodegeneration in AD. Our preliminary data suggest that ZCCHC17 may normally be responsible for mRNA splicing, and that this may be impaired when ZCCHC17 is dysfunctional. We are also investigating the localization of ZCCHC17 in the nucleus to identify proteins that ZCCHC17 may interact with. Finally, our preliminary data has linked possible drivers of AD pathology to ZCCHC17 dysfunction. **Conclusions:** Taken together, these data indicate that ZCCHC17 supports normal synaptic physiology, and further supports the hypothesis that ZCCHC17 impairment contributes to disease pathogenesis in AD.

**P3-174 EFFECT OF PHYSICAL EXERCISE ON MARKERS OF NEURONAL DYSFUNCTION IN CEREBROSPINAL FLUID IN PATIENTS WITH ALZHEIMER’S DISEASE**

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Background: Physical exercise has gained increasing focus as a potential mean to maintain cognitive function in patients with Alzheimer’s disease (AD). Alongside the markers of specific AD pathology (amyloid beta and tau), other pathologies such as neuronal damage and synaptic loss have been proposed as markers of the disease. Here we study the effect of physical exercise on biomarkers of neuronal and synaptic integrity.

Methods: Cerebrospinal fluid (CSF) from 51 AD subjects who participated in the randomized controlled trial ADEX study was analyzed for the concentration of neurofilament light (NFL), neurogranin (Ng), visinin-like protein-1 (VILIP-1) and chitinase-3-like protein 1 (YKL-40). Participants were subjected to either 16 weeks of moderate-to-high intensity exercise (n=25) or treatment as usual (“control group”, n=26), and CSF was collected before and after intervention. Results: No significant differences in CSF concentrations of VILIP-1, YKL-40, NFL and Ng were observed when comparing mean change from baseline between the exercise and control groups. Similarly, when classifying subjects based on their exercise levels, no significant changes were observed for the biomarkers in the control group compared to the High exercise group (80% of the exercise sessions with an intensity of 70% of maximum heart rate or above). Conclusions: These results are not supportive of a modulatory effect of physical exercise on the selected biomarkers of neuronal and synaptic integrity in patients with AD.

Poster Presentations: Tuesday, July 18, 2017

P3-176 F-ACTIN NANO-ARCHITECTURE IS COMPROMISED IN DENDRITIC SPINES OF PRIMARY NEURONS FROM APP/PS1 MICE AND IS RESTORED BY GLUTAREDOXIN-1

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Background: F-actin is the key cytoskeletal element present at the dendritic spines and its nano-organization plays a vital role in maintaining the shape and structure of spines under basal conditions as well as in alterations triggered by appropriate stimuli. Perturbations in F-actin level may therefore lead to altered nano-architecture of dendritic spines, potentially leading to synaptic dysfunction, which is a key feature in the pathogenesis of Alzheimer’s disease (AD).

Methods: Primary cortical neurons were derived from APPSwe/PS1DE9 (APP/PS1) mice and WT littermates at P1. All cultures were maintained for 15 to 17 days in-vitro (DIV) prior to fixation. Dil was used to detect dendritic spines. Actin-stain phalloidin 488 was used to label F-actin. Cells fixed in glutaraldehyde were used for direct stochastic reconstruction microscopy (dSTORM) after staining with Alexa647 phalloidin and immunostaining using against Homer1 antibody. Super-resolution images were acquired and processed using MetaMorph.

Results: Primary neurons from APP/PS1 mice exhibited loss of dendritic spines and F-actin levels were lowered when compared to WT. Strikingly, super-resolution imaging of dendritic spines revealed the arrangement of F-actin as periodically distributed outwardly radiating rods and this was significantly perturbed in spines under APP/PS1 primary neurons. Dil was used to detect dendritic spines. Actin-stain phalloidin 488 was used to label F-actin. Cells fixed in glutaraldehyde were used for direct stochastic reconstruction microscopy (dSTORM) after staining with Alexa647 phalloidin and immunostaining using against Homer1 antibody. Super-resolution images were acquired and processed using MetaMorph.

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Conclusions: This study establishes ROS-mediated glutathionylation of actin as one of the mechanisms leading to spine loss in APP/PS1 mice, which can be reversed by glutaredoxin1. We further describe that F-actin nano-assembly is distorted in dendritic spines very early in AD, leading to potential synaptic dysfunction.