Ressortforschungsberichte zum Strahlenschutz

International Workshop: Relationship between neurodegenerative diseases and magnetic field exposure - State of knowledge and research perspectives - Vorhaben 3617I02410

Auftragnehmer:
Valentum Kommunikation GmbH

Das Vorhaben wurde mit Mitteln des Bundesministeriums für Umwelt, Naturschutz und nukleare Sicherheit (BMU) und im Auftrag des Bundesamtes für Strahlenschutz (BfS) durchgeführt.

Bundesamt für Strahlenschutz

BfS-RESFOR-135/18

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Salzgitter, Juni 2018

Abschlussbericht

Vorhaben: 3617I02410

International Workshop: Relationship between neurodegenerative diseases and magnetic field exposure - State of knowledge and research perspectives

Auftragnehmer:
Valentum Kommunikation GmbH
Bischof-von-Henle Straße 2b
93051 Regensburg

Laufzeit des Vorhabens: Juli 2017 bis Januar 2018

Anlagen:
Veranstaltungsprogramm
Abstractband

1. Zielsetzung

Seit dem Ausstieg aus der Kernenergie und der zunehmenden Nutzung erneuerbarer Energien als Stromquelle wird der Stromnetzausbau bzw. die Umrüstung bestehender Netze in Deutschland weiter vorangetrieben. Diese Entwicklung kann dazu führen, dass die Bevölkerung vermehrt elektrischen und magnetischen Feldern ausgesetzt wird. Um die möglichen Auswirkungen genauer zu untersuchen, wurde vom Bundesamt für Strahlenschutz das Forschungsprogramm „Strahlenschutz beim Stromnetzausbau" ins Leben gerufen. Ein Forschungsaspekt, der dabei genauer untersucht wird, beschäftigt sich mit dem möglichen Zusammenhang zwischen niederfrequenten Magnetfeldern und neurodegenerativen Erkrankungen wie Alzheimer und ALS.

Im Rahmen einer 2,5-tägigen Veranstaltung wurde der aktuelle Forschungsstand aus unterschiedlichen wissenschaftlichen Perspektiven umfassend beleuchtet, um daraus mögliche weitere Forschungsansätze ableiten zu können.

1.1 Einzelzielsetzung

Unmittelbares Ziel der Veranstaltung war es, einen Überblick über den aktuellen Forschungsstand zu erhalten, neue Ansätze zu identifizieren, um auf deren Grundlage weitere Forschung aufzubauen. Für das Podium wurden internationale Rednerinnen und Redner aus verschiedenen Fachbereichen nach München eingeladen, um sich der Frage nach dem Zusammenhang zwischen Magnetfeldexposition und neurodegenerativen Erkrankungen von verschiedenen Seiten anzunähern. Ergänzt wurden sie durch ein internationales Teilnehmerfeld aus unterschiedlichen Fachbereichen.

Der Workshop wurde in acht inhaltlich aufeinander abgestimmte Sessions eingeteilt.

Die inhaltlichen Details und Vorbereitungen des Workshops wurden vom Bundesamt für Strahlenschutz und dem wissenschaftlichen Komitee erarbeitet. Die organisatorische Umsetzung erfolgte mit Unterstützung eines externen Dienstleisters (Valentum Kommunikation GmbH).

1.2 Voraussetzungen für den Workshop

Der Workshop fand im Tagungssaal des Salesianums, Don Bosco in München Haidhausen-Au statt. Der Veranstaltungsort ist sowohl vom Flughafen als auch vom Hauptbahnhof mit einer direkten S-Bahn Verbindung innerhalb von ca. 30 Minuten zu erreichen. Das Tagungscatering wurde durch den Veranstaltungsort geleistet.

1.3 Planung und Ablauf des Workshops

Die Aufgaben für die Organisation des Workshops wurden in drei Arbeitspakete eingeteilt.

AP 1: Planung des Workshops:

- Festlegung eines Veranstaltungstermins
- Auswahl eines Veranstaltungsortes und Einrichtung der notwendigen Infrastruktur (Technik, Catering)
- Einrichtung und Führung eines Tagungsbüros
- Erstellung einer Website und eines Flyers
- Rednermanagement
- Einladungsversand
- Strukturierung des Programms

- Laufende Organisation und Vorbereitung des Workshops:
    - Registrierung der Teilnehmerinnen und Teilnehmer
    - Gestaltung und Druck der Namensschilder
    - Gestaltung und Druck des Programmhefts sowie weiterer relevanter Dokumente
    - Betreuung der Rednerinnen und Redner sowie Gäste im Vorfeld
    - Koordination der Unterkunft der Rednerinnen und Redner
- Erstellung eines Abstractbandes

AP 2: Durchführung des Workshops

- Programmablauf siehe Anhang
- Koordination der Dienstleister vor Ort (Technik, Blumen, Catering, Conference Dinner)
- Betreuung der Rednerinnen und Redner sowie Gäste vor Ort

AP 3: Nachbereitung

- Bereitstellung der fotografischen Dokumentation der Veranstaltung
- Reisekostenabrechnungen
- Abschluss

1.4 Organisatoren

Die 2,5-tägige Veranstaltung „International Workshop: Relationship between neurodegenerative diseases and magnetic field exposure - State of knowledge and research perspectives“ wurde vom Bundesamt für Strahlenschutz (Ingolstädter Landstrasse 1 | 85764 Neuherberg) veranstaltet.

Die Organisation und praktische Durchführung wurde durch die Agentur Valentum Kommunikation GmbH (Bischof-von-Henle Straße 2b | 93051 Regensburg) unterstützt.

2. Durchführung des Workshops

2.1 Hintergrund

Alleiniger Veranstalter des Workshops, der vom 12. bis 14. Dezember 2017 in München stattfand, war das Bundesamt für Strahlenschutz im Auftrag des Bundesministeriums für Umwelt, Naturschutz, Bau und Reaktorsicherheit. Unmittelbar nach dem Auftaktgespräch am 04. Juli 2017 wurde die Veranstaltungswebseite https://www.neurodegenerative-workshop.de/ eingerichtet. Hier wurden laufend aktuelle Informationen zum Programm und dem Ablauf der Tagung sowie die Möglichkeit zur Registrierung bereitgestellt. Zudem wurde der Einladungsflyer als Download zur Verfügung gestellt und per E-Mail an interessierte Kontakte versandt.

2.2 Programm

Mit 21 Vorträgen von geladenen Rednern aus neun Ländern sowie zwei Kurzvorträgen (short talks) wurde das Programm des 2,5-tägigen Workshops gestaltet. Das Programm wurde in acht Einheiten gegliedert, die den Inhalt aufeinander aufbauend strukturierten:

- Session 1: Introduction to neurodegenerative diseases: What we know and what we do not know
- Session 2: Exposure assessment
- Session 3: Epidemiology: Low frequency magnetic fields as potential risk factors for neurodegenerative diseases
- Session 4: Etiology of ALS New Insights from animal models
- Session 5: Etiology of Alzheimer´s disease
- Session 6: Molecular pathways of ALS
- Session 7: Molecular Pathways of Alzheimer´s disease
- Session 8: Molecular responses to low frequency magnetic field exposure in cellular and animal models

Jede Einheit setzte sich aus den Präsentationen der Redner (20-35 Minuten) sowie Diskussionsrunden zusammen, die in Session 6 durch Kurzbeiträge seitens der Teilnehmer (10-minütige Short talks) ergänzt wurden. Interessierte Teilnehmer konnten sich im Vorfeld durch die Einreichung eines Abstracts um einen Beitrag zur Veranstaltung bewerben. Insgesamt wurden zwei Abstracts aus zwei Ländern eingereicht.

Zwischen den Programmpunkten konnte das Publikum Fragen zu den Präsentationen stellen und Probleme oder Streitpunkte diskutieren. Den Abschluss der Veranstaltung bildete eine ca. einstündige Diskussionsrunde. Teilnehmende, Redner und Veranstalter tauschten sich hier noch einmal über das Gehörte aus und erörterten gemeinsam Ansatzpunkte für die Weiterentwicklung der Forschung. Auf Basis des erhaltenen Feedbacks wird nun die weitere Vorgehensweise erarbeitet.

In den Programmpausen sowie bei einem gemeinsamen Conference Dinner am zweiten Veranstaltungstag konnten die Gäste den Austausch sowie das Networking im lockeren Rahmen fortsetzen.

Insgesamt nahmen 57 Personen aus 15 Ländern am Workshop teil. Die Teilnahme war für die Mitarbeiterinnen und Mitarbeiter des Bundesamts für Strahlenschutz kostenlos.

2.3 Beteiligte Akteure im Workshop

Geladene Redner

Nachname	Vorname	Institution	Land
Bertram	Lars	Institut für Neurogenetik, Universität Lübeck	Germany
Brandt	Roland	Department of Neurobiology	Germany
Clement	Albrecht	Institut für Pathobiochemie, Universität Mainz	Germany
Grosskreutz	Julian	Klinik für Neurologie, Universität Jena	Germany

Hooshmand	Babak	Karolinska Institutet	Sweden
Kheifets	Leeka	UCLA School of Public Health	USA
Kromhout	Hans	Institute for Risk Assessment, Utrecht University	Netherlands
Lagroye	Isabelle	Bioelectromagnetics Group, ENSCPB	France
Pal	Arun	Klinik und Poliklinik für Neurologie	Germany
Peters	Oliver	Klinik für Psychiatrie und Psychotherapie	Germany
Pietrzik	Claus	Universitätsmedizin Mainz	Germany
Rooney	James	Trinity College - School of Medicine	Ireland
Röösli	Martin	Swiss Tropical and Public Health Institute	Switzerland
Scekic-Zahirovic	Jelena	INSERM, University Strasbourg	France
Silva	Mike	Enertech Consultants, Campbell, CA, USA.	USA
Simko	Myrtill	SciProof International AB	Austria
Van den Bosch	Ludo	VIB KU	Belgium
Vergara	Ximena	Electric Power Research Institute,	USA
Verschaeve	Luc	Scientific Institute of Public Health	Belgium
Weishaupt	Jochen	Klinik für Neurologie	Germany
Weydt	Patrick	University of Bonn, Klinik für Neurodegenerative Erkrankungen	Germany

Referenten der Kurzvorträge

John Swanson, UK | Neurodegenerative diseases and magnetic-field exposure: Findings from the cohort study of UK electricity supply workers

Jonne Naarala, Finland | Extremely low frequency magnetic fields and Alzheimer´s disease: From mechanisms to epidemiology

Wissenschaftliches Kommitee

Albrecht Clement | Institute of Pathobiochemistry, University Medical Center of the Johannes Gutenberg, University, Mainz, Germany

Anne Dehos | Bundesamt für Strahlenschutz, Deutschland

Blanka Pophof | Bundesamt für Strahlenschutz, Deutschland

Ximena Vergara | Electric Power Research Institute, Energy & Environment Sector, USA

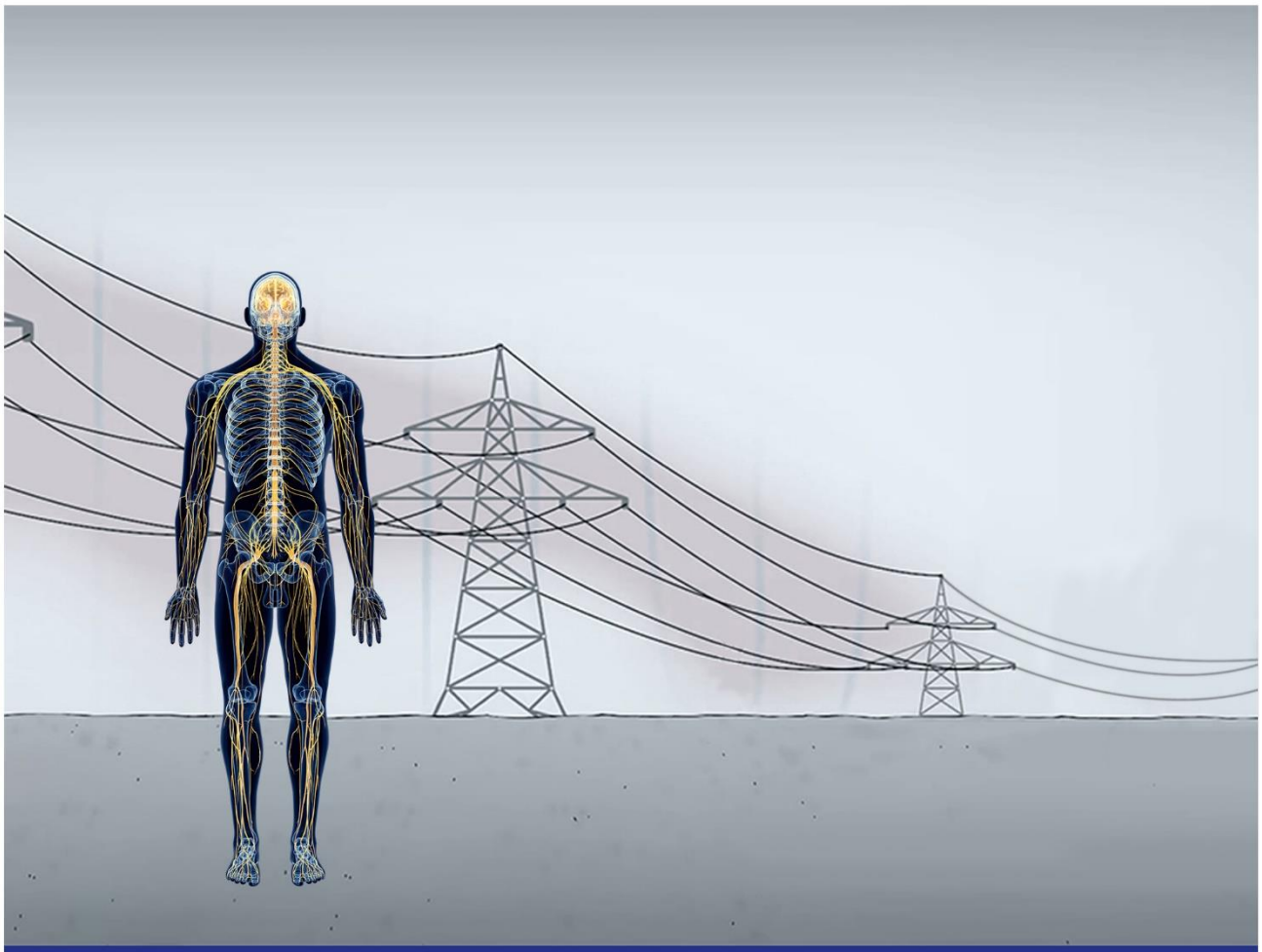
Gunde Ziegelberger | Bundesamt für Strahlenschutz, Deutschland

3. Ergebnisse

Für einen Überblick über die während des Workshops präsentierten Forschungsergebnisse sind im Anhang die eingereichten Abstracts beigefügt.

Kosten- und Zeitplanungen wurden eingehalten.

Bundesamt für Strahlenschutz



International Workshop:

Relationship between neurodegenerative diseases and magnetic field exposure – State of knowledge and research perspectives

12–14 December 2017 | Munich

Program & Abstracts

| RESPONSIBILITY FOR PEOPLE AND THE ENVIRONMENT |

Program

Tuesday | December 12

From 11:00	Arrival & registration | Welcome coffee & snacks
12:30 – 12:45	Official welcome *Michaela Kreuzer, Federal Office for Radiation Protection, Germany*

Session 1: Introduction to neurodegenerative diseases: What we know and what we do not know

Chair: Blanka Pophof | Federal Office for Radiation Protection, Germany

12:45 – 13:30	ALS: Current views on clinics, etiology and therapies *Julian Großkreutz, Germany*
13:30 – 14:15	Alzheimer´s disease: Current views on clinics, etiology and therapies *Oliver Peters, Germany*

Session 2: Exposure assessment

Chair: Jens Kuhne | Federal Office for Radiation Protection, Germany

14:15 – 14:45	Residential magnetic field exposure assessment *Mike Silva, USA*
14:45 – 15:15	Occupational exposure assessment - Electric work environment, magnetic fields, electric shocks, heavy metals and other exposures *Hans Kromhout, The Netherlands*
15:15 – 15:45	Coffee break

Session 3: Epidemiology: Low frequency magnetic fields as potential risk factors for neurodegenerative diseases

Chair: Gunde Ziegelberger | Federal Office for Radiation Protection, Germany

15:45 – 16:15	Residential MF and ALS/AD *Martin Röösli, Switzerland*
16:15 – 16:45	Occupational extremely low frequency magnetic fields exposure and neurodegenerative diseases *Ximena Vergara, USA*
16:45 – 17:15	ALS and the electric work environment: Electric shocks or magnetic fields? *Leeka Kheifets, USA*
From 18:00	Informal Get-together at "Klinglwirt" | Balanstraße 16, 81669 Munich

Wednesday | December 13

From 08:30	Arrival & registration

Session 4: Etiology of ALS

Chair: Gunde Ziegelberger | Federal Office for Radiation Protection, Germany

09:00 – 09:45	Lessons from prospective population based-registers in ALS *James Rooney, Ireland*
09:45 – 10:30	The genetics of ALS *Jochen Weishaupt, Germany*
10:30 – 11:00	Coffee break

Session 5: Etiology of Alzheimer´s disease

Chair: Blanka Pophof | Federal Office for Radiation Protection, Germany

11:00 – 11:45	The status of Alzheimer´s genetics: From GWAS to NGS and beyond *Lars Bertram, Germany*
11:45 – 12:30	Vitamin B12, folate and sulfur amino-acids as risk factors for Alzheimer´s disease and structural brain changes *Babak Hooshmand, Sweden*
12:30 – 14:00	Lunch break

Session 6: Molecular pathways of ALS

Chair: Albrecht Clement | University of Mainz, Germany

14:00 – 14:45	Molecular pathways and animal models in ALS *Ludo van den Bosch, Belgium*
14:45 – 15:15	FUS mouse and FUS pathogenesis *Jelena Scekic-Zahirovic, France*
15:15 – 15:45	Impaired DNA damage response signaling by FUS-NLS mutations leads to aggregate formation, distal axonopathy and neurodegeneration *Arun Pal, Germany*
15:45 – 16:15	Coffee break

Short talks

Chair: Anne Dehos | Federal Office for Radiation Protection, Germany

16:15 – 16:30	Neurodegenerative disease and magnetic-field exposure: Findings from the cohort study of UK electricity supply workers *John Swanson, UK*

16:30 – 16:45	Extremely low frequency magnetic fields and Alzheimer's disease: From mechanisms to epidemiology *Jonne Naarala, Finland*
From 18:00	Conference Dinner at "Dreigroschenkeller" | Lilienstr. 2, 81669 Munich

Thursday | December 14

From 08:00	Arrival & registration

Session 7: Molecular Pathways of Alzheimer´s disease

Chair: Blanka Pophof | Federal Office for Radiation Protection, Germany

08:30 – 09:00	The role of the blood-brain barrier in Alzheimer´s disease *Claus Pietrzik, Germany*
09:00 – 09:30	Inflammation in Alzheimer´s disease and ALS *Patrick Weydt, Germany*
09:30 – 10:00	Tau and Alzheimer´s disease: The neurodegenerative triad of synaptic changes, dendritic simplification and neuron loss *Roland Brandt, Germany*
10:00 – 10:30	Coffee break

Session 8: Molecular responses to low frequency magnetic field exposure in cellular and animal models

Chair: Gunde Ziegelberger | Federal Office for Radiation Protection, Germany

10:30 – 11:00	Extremely low frequency magnetic field exposure, inflammation and neurodegenerative diseases - In vivo and in vitro experimental evidence *Myrtill Simkó, Austria*
11:00 – 11:30	Potential effect of low-frequency magnetic fields (LF-MFs) on mouse models of amyotrophic lateral sclerosis and Alzheimer´s disease *Albrecht Clement, Germany*
11:30 – 12:00	ELF-EMF and in vitro and non-transgenic in vivo models of neurodegenerative diseases *Isabelle Lagroye, France*
12:00 – 12:30	Genetic damage following ELF-MF exposure in vitro: Relation with Alzheimer´s disease *Luc Verschaeve, Belgium*
12:30 – 13:30	Discussion and research perspectives
13:30 – 14:30	Buffet & Adjourn

Session 1: Introduction to neurodegenerative diseases: What we know and what we do not know

ALS: Current views on clinics, etiology and therapies

Julian Großkreutz | Department of Neurology, University Hospital Jena, Germany

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disorder of motor neurons, leading to death of the patient on average only 36 months after disease onset. ALS is characterized by heterogeneity at the clinical and genetic level. ALS causative mechanisms remain only partially understood and therapeutic strategies based on these mechanistic insights are largely ineffective.

The only drug available in Europe – Riluzole - extends the lifespan of ALS by 6 months, presumably by targeting disease modifying rather than disease causing targets. In the USA and Japan edavarone, an anti-oxidant, has been approved in addition which slightly slows functional loss in a subset of patients. To elucidate disease mechanisms, a vast array of epidemiologic, genetic, transcriptomic, metabolomic, proteomic, imaging and neurophysiological techniques have been applied in models and patients while the ALS immanent disease heterogeneity is being more and more overcome by quantification of disease progression and distribution in mathematical models.

As an all-encompassing explanation for the occurrence and phenotypic presentation of ALS remains elusive it is becoming clear that this complex disease represents a spectrum of many subtypes and genetic make-ups which challenge the development of an individualized ALS medicine, and insight into disease modifying factors rather than identification of a single mechanism will enhance our understanding of motor neuron degeneration and reveal potential therapeutic strategies.

Contact: Julian Großkreutz | julian.grosskreutz@med.uni-jena.de

Session 1: Introduction to neurodegenerative diseases: What we know and what we do not know

Alzheimer´s disease: Current views on clinics, etiology and therapies

Oliver Peters | Research institute for neurodegenerative diseases, Charité Berlin, Germany

Alzheimer´s disease (AD) is a chronic neurodegenerative disorder finally leading to dementia. Since new diagnostic tools, like neurochemical analyses of the cerebral spinal fluid (CSF) and Amyloid-PET-imaging have become available, early diagnosis has become much more reliable. Even diagnosis of preclinical stages, without any clinical symptoms like memory problems, but at risk to develop Alzheimer´s dementia in the future have been defined in ongoing clinical research.

Although the complete neuropathophysiology of Alzheimer´s disease is still unknown, so called surrogate markers, like A-beta and Tau in CSF and Amyloid-plaques in PET, provide a high diagnostic sensitivity and specificity in early clinical disease stages. While symptomatic drugs, enhancing cognitive function in dementia are available since many years, all attempts to establish disease modifying therapies have failed so far. Clinical trials testing new drugs focusing on early disease stages with the aim to slow down disease progression are underway and results from numerous Phase III-studies are expected to be published over the next years.

Contact: Oliver Peters | oliver.peters@charite.de

Session 2: Exposure assessment

Residential magnetic field exposure assessment

J. Michael Silva | Enertech Consultants, USA

A small number of epidemiological studies have examined the association between power frequency (50/60 Hz) residential magnetic field (MF) exposure and neurodegenerative disease (NDD) endpoints. Exposure assessment for these NDD studies has primarily used distance to overhead transmission lines, although a few have used calculated MF levels. Previous residential studies of different health outcomes have used a variety of proxy measures for MF exposure, including: wire configuration codes, distance from nearby transmission lines, present-day measurements, and calculated MF. If the goal is to assess historic residential MF exposure for the time period of interest in epidemiologic studies, then some important questions arise:

- What is the appropriate exposure metric in the absence of a biological mechanism?
- Does residential exposure assessment alone capture all relevant exposure?
- What is the most reliable proxy to evaluate historic residential MF exposure?

Transmission line magnetic field determinants are primarily distance, conductor configuration, and electrical loading. These factors interact in complex ways for MF close to transmission lines (< 50 m), but may be less important farther away. In addition, without an established biological interaction mechanism there is no clear metric to characterize MF exposure with a single value. The mean or time-weighted-average (TWA) of MF has emerged as the de facto standard for exposure assessment. However, other MF exposure metrics have been proposed, including peak, time above some threshold, geometric mean, rate of change, MF stability, and higher frequency transients. It also may be important for NDD studies that some occupations have larger exposures at work than at home.

Recent studies of residential exposure for other health endpoints (childhood leukemia) have relied on calculated historic MF using appropriate historic loads and line configurations to perform calculations. Does calculated MF improve on distance alone to characterize residential exposure? The correlation between distance and calculated MF is limited and appears to be not very good. If the primary determinants of calculated MF are accurately quantified for the calculations, it would be expected that calculated MF would be better than distance alone since it also includes conductor configuration and historic loading. However, distance alone may capture a factor(s) associated with NDD, but unrelated to MF (e.g. SES, traffic pollution, pesticides, population density, etc.).

Contact: J. Michael Silva| msilva@enertech.net

Session 2: Exposure assessment

Occupational exposure assessment for epidemiological studies – Electric work environment, magnetic fields, electric shocks, heavy metals and other exposures

Hans Kromhout | Environmental Epidemiology Division, Institute for Risk Assessment Sciences, Utrecht University, Netherlands

Exposure assessment and assignment for individuals enrolled in occupational epidemiological studies are crucial for informative results of such studies. Random error in exposure assessment will often result in attenuation of an exposure - response association while response bias might result in spurious associations.

In recent years new tools for occupational exposure assessment and assignment have been developed in the field of health effects of occupational exposure to electromagnetic fields. Job-exposure matrices for extremely low frequency electromagnetic fields and electrical shocks have enabled disentangling the effects of hypothesized exposures linked to negative health outcome. In my presentation I will present the possibilities and challenges of different methods for exposure assessment ranging from proxies like job-title, via self-reported exposures to job-exposure matrices and measurements. It will become clear that the methods differ because of the health endpoint studied (chronic or acute health effects), the study design chosen (cohort, cross-sectional or case-control study) and access to the study population.

I will also show that in meta-analyses of the results of epidemiological studies quality of the exposure assessment will make a distinct difference in the reported pooled risk-estimate. Recent studies performed within the realm of the Netherlands Research Programme Electromagnetic Fields and Health Research 2006-2019 will form the basis for showing how crucial exposure assessment and assignment is in the process of having an informative study.

Contact: Hans Kromhout| h.kromhout@uu.nl

Session 3: Epidemiology: Low frequency magnetic fields as potential risk factors for neurodegenerative diseases

Residential MF and ALS/AD

Martin Röösli | Swiss Tropical and Public Health Institute, Switzerland

Average residential extremely low frequency magnetic fields (ELF-MF) exposure is typically lower than in highly exposed occupational settings. However, people living in proximity to high voltage power lines are exposed for longer time periods and this has triggered epidemiological research to evaluate a potential link between residential ELF-MF and neurodegenerative diseases. The few studies published to date are mainly case-control studies. Most studies used distance to the nearest high voltage power line as their main exposure proxy. Outcome was either obtained from death certificates or hospital discharge records.

None of the five studies on amyotrophic lateral sclerosis (ALS) or motor neuron diseases found elevated ALS in relation to residential ELF-MF based on a total of 27 exposed cases. Only two studies addressed Alzheimer's disease (AD), both of them with an overall absence of association but elevated risks in some subgroup analyses. In the nationwide Swiss cohort study restricted to the population living for at least 15 years at the identical place, a doubled risk was observed for people living within 50 m of a highest voltage power line (≠220 kV) based on 15 exposed cases.

In the Danish case-control study, the only significantly elevated odds ratio was observed in 65 to 75 year old people diagnosed after 2002 based on 9 cases and 23 controls. These two studies also considered Parkinson's disease and multiple sclerosis without any indications for elevated risks from ELF-MF. In conclusion, the few epidemiological studies published to date do not suggest that exposure to residential ELF-MF increases the risk to develop a neurodegenerative disease.

Contact: Martin Röösli | martin.roosli@swisstph.ch

Session 3: Epidemiology: Low frequency magnetic fields as potential risk factors for neurodegenerative diseases

Occupational extremely low frequency magnetic fields exposure and neurodegenerative diseases

Ximena Vergara | Electric Power Research Institute, USA

Background: Longer human lifespans lead to increased prevalence of neurodegenerative diseases (NDD) impacting workforce productivity and the economy. Clues from worker populations, generally highly exposed to agents compared to the general population, often prompt pursuit of research on potential residential exposures. The predominant focus of occupational extremely low frequency magnetic fields (ELF-MF) research has been on Alzheimer's (AD) and motor neuron diseases (MND), such as amyotrophic lateral sclerosis (ALS). In this presentation, I use a systematic review of the occupational ELF-MF and NDD literature as a basis for understanding and update it with recently published articles.

Approach: For the meta-analysis, we searched for peer-reviewed articles published prior to January 12, 2012. A total of 197 potentially relevant articles on NDD were identified, and 3 were added from article references. Standardized procedures were developed to extract both study characteristics and relative-risk estimates. Publication bias, was evaluated using the Egger regression asymmetry test for funnel plots and Begg-Mazumdar test. We examined the influence of each specific study on the overall estimate by omitting one study at a time.

Results: Of the 42 qualified studies, 20 were of Alzheimer's disease, 21 of MND including ALS, 18 of Parkinson's disease, 9 of dementia and 5 of multiple sclerosis. All included studies were either case-control (n=27) or cohort design (n=15). Nineteen occupational studies came from the U.S., 15 from Nordic countries, with additional studies from other countries. Nearly 40% of studies examined prevalence and about 30% examined mortality, with most diagnoses from clinical pathology/diagnostic criteria (n=30). Of the 22 MND or AD case-control studies, few excluded other NDD from the controls (n=8) and few used population controls (n=5). Exposure in 15 studies was based on a representative job, of these 6 studies classified MF levels by JEM and 3 studies using industrial hygiene assessment. Small associations for MND (RRRE = 1.26, 95% CI: 1.10 – 1.44) and AD (RRRE = 1.27, 95% CI: 1.15 – 1.40) were present in both fixed and random effects (RE) models. Overall, we observed no association between MND and MF levels, but elevated relative risks for MND by occupational titles. The opposite was observed for AD; elevated relative risks for AD by MF levels, but not for occupational titles.

Summary: Results of this meta-analysis do not support ELF-MF as an explanation of the associations between occupational titles and MND. While elevated associations between ELF-MF and AD were observed, disease misclassification and exposure misclassification were present in those studies. Since this meta-analysis, several other studies on occupational ELF-MF and NDD have been published and will be briefly reviewed.

Contact: Ximena Vergara | xvergara@epri.com

Session 3: Epidemiology: Low frequency magnetic fields as potential risk factors for neurodegenerative diseases

ALS and the electric work environment: Electric shocks or magnetic fields?

Leeka Kheifets | Fielding School of Public Health Department of Epidemiology, University of California Los Angeles, USA

The earlier studies on amyotrophic lateral sclerosis (ALS) examined the possible link between electric shocks and ALS. After the first study in 1964 suggested a plausible relationship, two subsequent studies from Japan, where the prevalence of electrical work (as recorded in the medical history) and of electrical shock was low, failed to provide any support for the hypothesis. A meta-analysis of 21 occupational studies found a small risk OR= 1.3, 95% CI = 1.1-1.4, which was largely confined to associations based on electrical occupations rather than magnetic field measurements.

Work in the utility industry, as well as in other electrical occupations, carries a risk of experiencing electric shocks, thus shocks have been suggested as a possible confounder. Although there is modest epidemiological evidence to suggest that employment in electrical occupations may increase the risk of ALS, separating whether the increased risk is due to higher probability of receiving electric shocks or from the increased exposure to long-term exposure to magnetic fields is difficult.

Several recent occupational studies examined both magnetic fields and electric shocks based on job exposure matrices with inconsistent results. In this presentation, I will present and compare available evidence examining the associations between magnetic fields, shocks and ALS. Studies of ALS that can distinguish between electric shocks and magnetic fields, including pooled analysis of such studies, are needed.

Contact: Leeka Kheifets | kheifets@ucla.edu

Session 4: Etiology of ALS

Lessons from prospective population based-registers in ALS

James Rooney | School of Medicine, Trinity College, Ireland

Prospective population based-registers of amyotrophic lateral sclerosis (ALS) have operated in Europe for over two decades, and have provided important insights into our understanding of ALS. Population-based registers identify and characterize all cases of the disease, including those that might otherwise be neglected – thus improving our understanding of the incidence, prevalence, and phenotype of ALS. Multiple data sources are recognised to provide the best mechanism for complete data capture and to help to avoid ascertainment biases. Furthermore, common operating principles underlie ALS registers in Europe and, together with the concept of "core clinical data", facilitate international collaboration. Prospective population-based registers are necessary to provide comprehensive data on the whole phenotypic spectrum of ALS, and can guide planning of health services. In addition, they facilitate novel study designs – including the comparison of different treatment models and modelling of disease pathogenesis.

In this lecture, I will review the lessons learned from population-based ALS registers operating in Europe for over two decades, highlighting key register design features, identification and management of bias, and I will review study designs that are best performed using data from population based registers including spatial epidemiological studies, comparison of care models and multi-step models of disease aetiology.

Contact: James Rooney | ROONEYJ4@tcd.ie

Session 4: Etiology of ALS

The genetics of ALS

Jochen Weishaupt | Neurology Department, Ulm University, Germany

Amyotrophic Lateral Sclerosis (ALS) is a multisystem neurodegeneration clinically characterized by a predominant degeneration of motor neurons and progressive weakness of voluntarily innervated muscles, including muscles of the respiratory apparatus. This leads to almost complete paresis after a few years, and death is usually by respiratory failure. The most important known risk factor for ALS, besides increased age, is a positive family history. Overall, a positive family history for ALS or the neuropathologically and genetically linked disease frontotemporal dementia (FTD) is recognized in approximately 5-10% of all ALS patients.

However, a higher contribution of genetic factors can be assumed as inheritance may be missed due to incomplete penetrance, incomplete family history or an oligogenic mode of inheritance. The advent of next generation sequencing lead to a wave of novel ALS-related genes. Altogether, mutations in more than 25 genes have been suggested to cause ALS or FTD in a mostly autosomal-dominant manner. The ALS/FTD genes discovered in recent years seem to be quite diverse at first glance. However, their physiological functions and properties can be grouped according to few common functional denominators, e.g. RNA metabolism or cytoskeletal functions.

In this talk, I will summarize the current state of knowledge of ALS genetics, and outline the main conclusions that can be drawn with regard to principle mechanisms of ALS pathogenesis.

Contact: Jochen Weishaupt | jochen.weishaupt@uni-ulm.de

Session 5: Etiology of Alzheimer´s disease

The status of Alzheimer's genetics: From GWAS to NGS and beyond

Lars Bertram | Lübeck Interdisciplinary Platform for Genome Analytics, University of Lübeck, Germany | School of Public Health, Imperial College London, UK

It has been estimated that up to 80% of Alzheimer's disease susceptibility is due to genetic factors. Over the past decade, large-scale and unbiased studies of ever increasing sample size (i.e. genome-wide association studies [GWAS]) and/or increasing genomic resolution (i.e. via next-generation sequencing [NGS]) have identified an ever increasing number of loci underlying the genetic liability of the disease. In my presentation I will present an up-to-date report of the genetics of Alzheimer's highlighting exciting recent findings from both GWAS and NGS-based studies. Furthermore, I will provide a brief outlook on the future of Alzheimer's genetics/genomics research including studies aimed deciphering the potential role of epigenetic mechanisms.

Contact: Lars Bertram | lars.bertram@uni-luebeck.de

Session 5: Etiology of Alzheimer´s disease

Vitamin B12, folate and sulfur amino-acids as risk factors in Alzheimer´s disease and structural brain changes

Babak Hooshmand, Alina Solomon, Laura Fratiglioni, Miia Kivipelto | Aging Research Center, Karolinska Institute, Sweden

Elevated concentrations of tHcy or low concentrations of vitamin B12 are common conditions in older adults and may be associated with structural brain changes impairment of cognition, and to dementia. There are several biological plausible mechanisms for such associations and vitamin B12 and folate may be considered as strong candidates for prevention of dementia. I will present and discuss findings from longitudinal studies as well as randomized controlled trials for such associations. I will also provide some clinical and research implications for future works on this topic.

Contact: Babak Hooshmand | Babak.Hooshmand@ki.se

Session 6: Molecular pathways of ALS

Molecular pathways and animal models in ALS

Ludo van den Bosch | Department of Neurosciences, Laboratory of Neurobiology, KU Leuven University, Belgium

Using different in vitro and in vivo models, we investigate the molecular pathways involved in the selective death of motor neurons, which is the hallmark of amyotrophic lateral sclerosis (ALS). The in vitro models include cell lines as well as motor neurons differentiated from induced pluripotent stem cells (iPSCs) obtained from fibroblasts of ALS patients. The in vivo models range from small animals, like Drosophila and zebrafish, to rodents. Except for some of the iPSC-derived in vitro models, all our models are based on genetic causes of ALS, the most important ones being mutations in SOD1, FUS, TARDBP and hexanucleotide repeats in C9orf72. Apart from studying the pathogenic mechanisms in these models, we also focus on the genetic modifying factors that influence the disease course as these could lead to interesting therapeutic strategies.

A typical feature of neurodegenerative disorders in general and of ALS in particular is the presence of protein inclusions. In ALS, the predominant pathological species detected in these aggregates are RNA-binding proteins, including FUS or TDP-43, the gene product of the TARDBP gene. These RNA-binding proteins are depleted from their normal nuclear localization, mislocalize to the cytoplasm and ultimately form macroscopic aggregates. These key pathological features suggest a stepwise mechanism.

The first question is how this pathological cascade is initiated. In most patients, and especially in sporadic cases, this is not yet clear. Recent data on C9orf72 ALS models point at an important role for the nuclear transport system. We observed that the arginine-containing dipeptide repeat proteins (DPRs), which can be translated in a non-ATG mediated way from the hexanucleotide repeat expansions in C9orf72, can cause toxicity. This toxicity can be modulated by interfering with the expression of importins, exportins, Ran-GTP cycle regulators, and nuclear pore components.

Once mislocalized into the cytoplasm, these RNA-binding proteins can become part of stress granules. The arginine-rich domains of these proteins play a crucial role in this process. We observed that the arginine-rich DPRs can also undergo liquid-liquid phase separations. Moreover, these DPRs are able to induce spontaneous stress granule assembly in cells and they can also induce phase separation of a large set of proteins involved in RNA metabolism. These stress granules are generally considered as the stepping stone towards the pathological aggregates containing different RNA-binding proteins.

Altogether, both arginine-rich DPRs and RNA-binding proteins seem to play an important role in the pathogenesis of C9orf72 ALS. Moreover, disturbances in nucleocytoplasmic transport could initiate a cascade of events ultimately leading to the formation of cytoplasmic aggregates containing RNA-binding proteins.

Contact: Ludo Van Den Bosch | ludo.vandenbosch@kuleuven.vib.be

Session 6: Molecular pathways of ALS

FUS mouse and FUS pathogenesis

Jelena Scekic-Zahirovic[1], Hajer El Oussini[1], Stéphane Dieterlé[1], Jérome Sinniger[1], Immaculada Sanjuan-Ruiz[1], Raphaelle Cassel[1], Sylvie Dirrig-Grosch[1], Marie-Christine Birling[4], Anne-Laurette Boutillier[5], Jean Christophe Cassel[5], Frédérique René[1], Caroline Rouaux[1], Erik Storkebaum[2], Clotilde Lagier-Tourenne[3] and Luc Dupuis[1]

1 INSERM U1118, Université de Strasbourg, Faculte de medecine, Strasbourg, France
2 Molecular Neurogenetics laboratory, Max Planck Institute, Münster, Germany
3 Department of Neurosciences, Ludwig Institute for Cancer Research, University of California, San Diego, USA
4 Institut Clinique de la Souris, Illkirch-Graffenstaden, France
5 LNCA, UMR7364 CNRS Université de Strasbourg, Strasbourg, France

Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) are now consideredas a unique clinicopathological spectrum referred to as ALS/FTD. Cytoplasmic aggregation of the physiologically nuclear FUS (fused in sarcoma) protein is a hallmark feature of a subset of ALS/FTD cases.

To unravel whether the critical pathogenic event relies on a loss of FUS normal nuclear functions, a toxic gain of function of FUS in the cytoplasm, or a combination of both, we have generated a novel conditional knock-in animal model relevant to ALS, that constitutively expresses a truncated Fus gene from the endogenous murin Fus locus. The truncated gene, noted Fus←NLS, lacks the sequence encoding the nuclear localization signal (NLS) of FUS protein, preventing FUS from being transported to the nucleus, and mimicking the pathology of Fus mutant carriers that develop ALS with a very early onset and rapid progression. Our data showed that complete cytoplasmic mislocalization of truncated FUS protein in FusΔNLS/ΔNLS mice within lower motor neurons (LMN), is a major determinant of motor neuron degeneration via toxic gain of function mechanism.

Next, to better mimic the Human FUS pathology, as ALS-FUS patients with rare exceptions carry only one mutated allele of Fus and present with a partial re-localization of FUS from the nucleus only to both the nucleus and the cytoplasm, we characterized the phenotype of heterozygous FusΔNLS/+ animals. As well, partial mislocalization of truncated FUS protein was sufficient to trigger a progressive loss of LMN. Importantly, FusΔNLS/+ animals develop, over time, a mild progressive motor deficit, along with neuropathological changes that faithfully recapitulate several key aspects of ALS-FUS. Similar to the homozygous mice, restoring the expression of the wild type gene by Cre-mediated recombination within the ChAT-expressing neurons rescued LMN degeneration demonstrating that toxic gain of function is cell autonomous. However, this was not sufficient to counteract the progression of the motor impairment confirming the necessary contribution of other cell types to this motor phenotype through non-cell autonomous mechanisms.

Since FUS mislocalization and aggregation are also observed in a subset of FTD patients, we next asked whether FusΔNLS/+ mice might develop FTD-like phenotype. Our results demonstrated that FusΔNLS/+ animals presented with behavioural and cognitive impairments indicative for FTD. Consistently, we observed significant progressive frontotemporal lobe atrophy. Histopathological analysis of these brains is currently ongoing to characterize the neuroanatomical substrate of this atrophy. Altogether, suggested that mislocalization of truncated FUS protein is also detrimental for proper cortical functions.

These studies allowed the elucidation of mechanisms underlying FUS pathogenesis in ALS/FTD, and will hopefully lead to development of therapies for these devastating diseases.

Contact: Jelena Scekic-Zahirovic | jelena.scekic-zahirovic@inserm.fr

Session 6: Molecular pathways of ALS

Impaired DNA damage response signaling by FUS-NLS mutations leads to aggregate formation, distal axonopathy and neurodegeneration

Arun Pal | Faculty of Medicine Carl Gustav Carus, TU Dresden, Germany

Our overall aim is disease modelling of Amyotrophic Lateral Sklerosis (ALS), a fatal disease of cortical and spinal motor neuron degeneration leading to muscle paralysis. We use neuronal progenitor cells (NPCs) and fully differentiated motor neurons (MNs) derived from inducible pluripotent stem cells (iPSCs) obtained from ALS patients with well characterized mutations in the nuclear location sequence (NLS) of the Fused In Sarcoma (FUS) gene.

FUS aggregates are pathological hallmarks of FUS-ALS, and physiological function depends on proper shuttling between the nucleus and cytoplasm. The initial event in the pathophysiology of FUS-ALS, however, remains enigmatic. Using MN lines with GFP-tagged endogenous FUS, we revealed by Laser microirradiation and live video microscopy of compartmentalized cultures a compromised DNA damage response (DDR) along with cytoplasmic FUS mislocalization and aggregation caused by the mutant NLS. These failures in DDR caused in turn further downstream defects in distal axonal organelle trafficking and mitochondria function through a yet uncharacterized long-distance nucleo-axonal crosstalk. Overall, these pathogenic insults cumulated in premature neurodegeneration, i.e. distal dying back of axons. Targeting DDR signaling could lead to novel therapeutic routes for ameliorating ALS.

We found that the underlying key players of deficient DDR in FUS-ALS are well known from oncology, e.g. PARP, DNA-PK, KU70, KU80, LIG1, thereby pointing to a common upstream mechanistic denominator of cancer and neurodegeneration. Thus, patients of both cancer and ALS (and other neurodegenerative disorders as well) exhibit increased radio sensitivity, i.e. need to limit themselves to ionizing radiation and x-ray applications. By the end of my talk I will openly discuss if and how these findings relate to magnetic field exposure concerns as well.

Contact: Arun Pal | Arun.Pal@uniklinikum-dresden.de

Session 6: Short talks

Neurodegenerative disease and magnetic-field exposure: Findings from the cohort study of UK electricity supply workers

John Swanson | National Grid UK, University of Birmingham, UK

The mortality experienced by a cohort of 73,051 employees of the former Central Electricity Generating Board of England and Wales (hired in the period 1952-82, employed for at least six months, with some employment after 1973) was investigated for the period 1973-2010. The baseline (reference) exposure category was lifetime occupational exposure of less than 2.5 uT.year. For Alzheimer's Disease, there was no elevation of risk at the highest exposures (relative risk (RR) for exposure >=20.0 uT.year 0.78, 95% CI 0.36 to 1.71, 7 cases) and no positive trend of risks increasing with exposure. Similarly, for Motor Neurone Disease, RR for exposure >=20.0 uT.year 1.32, 95% CI 0.55 to 3.16 (6 cases) with no significant positive trend of MND risks increasing with exposure. For both diseases there were also no statistically significant trends when the analysis was limited to recent or distant exposure to magnetic fields.

The findings are consistent with the hypothesis that occupational magnetic field exposures are not causally related to neurodegenerative diseases.

A distinctive feature of this work is that exposure was not estimated solely from job (via a JEM). Detailed calculations, using information on the layout of magnetic field sources within specific sites and calendar year as well as job, were performed to enable an improved exposure assessment to be made. "Job", although convenient to use and ubiquitous, can be a poor predictor of exposure to magnetic fields. This work expands the normal job-exposure matrix into a job-site-year-exposure matrix.

Contact: John Swanson | john.swanson@physics.org

Session 6: Short talks

Extremely low frequency magnetic fields and Alzheimer's disease: From mechanisms to epidemiology

J. Naarala, P. Roivainen, J. Luukkonen, M.W. Khan, H. Tanila and J. Juutilainen | Department of Environmental and Biological Sciences and A.I. Virtanen Institute, University of Eastern Finland, Finland

Some epidemiological studies suggest that environmental extremely low frequency (ELF) magnetic fields (MF) may be associated with increased risk of Alzheimer's disease (AD). However, existence of a causal relationship is unclear; the epidemiological findings are inconsistent, animal studies have not provided supporting evidence, and a generally accepted mechanism for the link is lacking. Neuroscience is one of the major research areas of the University of Eastern Finland, with many research groups focusing on various aspects of AD. We plan to study the possible link between ELF MFs and AD using multiple approaches from in vitro studies to epidemiology.

Our epidemiological approach is based on indoor transformer stations in residential buildings. Such stations offer a feasible basis for designing epidemiological studies that avoid selection bias, minimize confounding factors and include people exposed to relatively strong ELF MFs (1). We have compiled a register of Finnish people who live or have lived in buildings with transformer. This register can be linked to Drug Reimbursement Register in order to reliably identify cohort members who have AD.

The planned in vivo studies will include experiments with an AD model, the transgenic APP/PS1 mice. In the Neurobiology of Memory Laboratory (2), we can fully characterize the phenotype of the MF-exposed/sham-exposed mice through a broad behavioral test battery, and analyze the mouse brains for, e.g., hallmarks of AD pathology, such as amyloid deposits, tau phosphorylation and neuroinflammation.

Our ongoing in vitro studies focus on magnetosensitive radical pair reactions in cryptochromes (CRY) (apparently involved in magnetoreception in animals) as a possible basis for adverse health effects of environmental ELF MFs (3). Although possible carcinogenic effects were the main motivation for these studies, there are many links to AD as well. CRY proteins are a part of the circadian clock system, and also involved in regulation of cell cycle and DNA damage responses and the level of reactive oxygen species (ROS); disturbances of the circadian rhythms, DNA damage, DNA repair and ROS have been implicated in the biological processes leading to AD. There is evidence of ELF MF effects on relevant biological processes in cells with neural or glial origin (4-6).

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Contact: Jonne Naarala | jonne.naarala@uef.fi

Session 7: Molecular Pathways of Alzheimer´s disease

The role of the blood brain barrier in Alzheimer Disease

Steffen Storck[1], Anika Hartz[2], Jens Pahnke[3], Claus U. Pietrzik[4]

1 University Medical Center of the Johannes Gutenberg-University Mainz, Institute for Pathobiochemistry, Mainz, Germany
2 University of Kentucky, Sanders-Brown Center on Aging Department of Pharmacology and Nutritional Sciences, Lexington, USA
3 University of Oslo (UiO) & Oslo University Hospital (OUS), Department of Neuro-/Pathology, Oslo, Norway
4 Claus U. Pietrzik at the University Medical Center of the Johannes Gutenberg-University Mainz, Institute for Pathobiochemistry, Mainz, Germany

According to the neurovascular hypothesis, impaired clearance of the amyloid-beta (Aβ) peptide across the blood-brain barrier (BBB) contributes to Alzheimer's disease (AD) pathology. The low-density lipoprotein receptor-related protein-1 (LRP1) decreases with age and has been hypothesized to contribute to reduced metabolite clearance at the BBB, leading to beta-amyloid (Aβ) accumulation, a key event in AD pathology. To test this hypothesis, we engineered mice with selective knockout of Lrp1 in the brain endothelium and choroid plexus (CP) epithelium (Lrp1BE-/-). We used in vitro and in vivo methods to quantify the rate of Aβ clearance across the BBB. With a novel Slco1c1-CreERT2 mouse, we generated the first brain endothelial-specific Lrp1 knockout mouse to accurately evaluate LRP1-mediated Aβ BBB-clearance in vivo. Using stereotactical injections of physiological concentrations of radiolabeled Aβ peptides, we were able to quantify the rate of LRP1 mediated clearance at the BBB in vivo. Crossing the LRP1 KO mice to the 5xFAD mouse model resulted in reduced plasma Aβ and elevated soluble brain Aβ leading to aggravated spatial learning and memory deficits, thus, emphasizing the importance of systemic Aβ elimination via the BBB. We found that endothelial LRP1 is a major receptor for Aβ BBB clearance leading to cognitive impairment in the 5xFAD mouse model of AD. As recombination in Lrp1BE-/- mice occurs in epithelial cells of the CP, we further studied LRP1-mediated Aβ clearance across the blood-cerebrospinal fluid barrier.

However, conflicting findings on the involvement of different Aβ transporters at the BBB and their expression in brain endothelium have questioned the role of LRP1 and Pgp at the BBB. By combining primary mouse brain endothelial cells from these animals with Pgp inhibitors, we are able to identify the role of each transporter at the BBB for Aβ clearance in vitro. Dissecting the function of these transporters may provide new approaches for treatment and prevention of Aβ brain accumulation in AD.

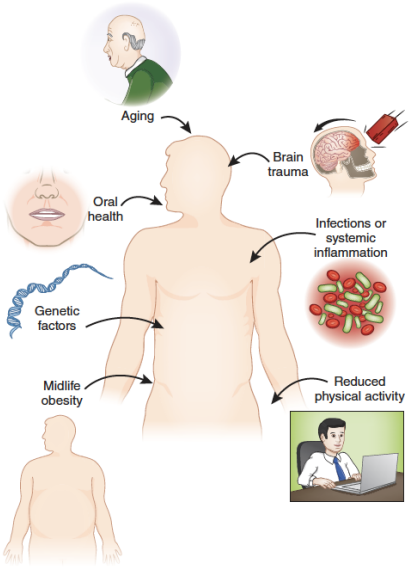
Contact: Claus Pietrzik | pietrzik@uni-mainz.de

Session 7: Molecular Pathways of Alzheimer´s disease

Inflammation in Alzheimer's disease and ALS

Patrick Weydt | Department of Neurodegenerative Diseases and Gerontopsychiatry, University of Bonn Medical Center, Germany

Over the past few decades, research on Alzheimer's disease (AD) has focused on pathomechanisms linked to two of the major pathological hallmarks of extracellular deposition of beta-amyloid peptides and intra-neuronal formation of neurofibrils. Recently a third disease component, the neuroinflammatory reaction mediated by cerebral innate immune cells, has entered the spotlight, prompted by findings from genetic, pre-clinical and clinical studies. Various proteins that arise during neurodegeneration, including beta-amyloid, tau, heat shock proteins, chromogranin among others act as danger-associated molecular patterns, that – upon engagement of pattern recognition receptors – induce inflammatory signaling pathways and ultimately lead to the production and release of immune mediators. These may have beneficial effects, but ultimately compromise neuronal function and cause cell death. We will provide an overview of our current understanding of AD related immune processes. We describe the principal cellular and molecular players in inflammation as they pertain to AD, examine modifying factors and discuss potential future therapeutic targets. In keeping with the interdisciplinary spirit of the workshop we will also briefly highlight similarities and differences in the neuroinflammatory response between AD and ALS.



Source: From Heneka et al. Nat Imm. 2015

Contact: Patrick Weydt | patrick.weydt@ukbonn.de

Session 7: Molecular Pathways of Alzheimer´s disease

Tau and Alzheimer: The neurodegenerative triad of synaptic changes, dendritic simplification and neuron loss

Roland Brandt | Department of Neurobiology, University of Osnabrück, Germany

Tau is a neuronal microtubule-associated protein that has been implicated in the regulation of axonal microtubule assembly. Pathologic changes of tau are involved in several diseases collectively called tauopathies, which include Alzheimer's disease as the most common cause of dementia of the elderly. In this presentation, tau's function in health and its malfunction in disease will be introduced. It will be shown that tau interacts with neuronal microtubules by a highly dynamic "kiss and hop" mechanism, which allows modulation of microtubule assembly without interfering with axonal transport processes. It will be introduced that tau is an intrinsically disordered protein, which interacts with many other cellular components including components of the axonal plasma membrane, and that pathologic processes may induce subtle changes in microtubule interaction and tau's binding to other cellular components. Evidence will be provided that tau is also involved in modulation of neuronal network activities by influencing pre- and postsynaptic mechanisms involved in learning and memory. Finally, tau's involvement in the neurodegenerative triad of synaptic loss, dendritic simplification and neuron loss will be discussed and how environmental changes may affect neurodegenerative processes by affecting tau expression, tau modification and regulation of microtubule dynamics.

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Contact: Roland Brandt | brandt@biologie.uni-osnabrueck.de

Session 8: Molecular responses to low frequency magnetic field exposure in cellular and animal models

Extremely low frequency magnetic field exposure, inflammation and neurodegenerative diseases - in vivo and in vitro experimental evidence

Myrtill Simkó | SciProof International AB, Sweden

Possible health consequences of exposure to extremely low frequency magnetic fields (ELF-MF) have included the area of neurodegenerative diseases (NDD), where epidemiological evidence suggests a correlation between MF exposure and Alzheimer's disease (AD). The question is, if there is any mechanistic support for a causal connection between MF-exposure and NDD. The hypothesis is that ELF-MF exposure can promote inflammation processes and thus influence the progression of NDD. This hypothesis is based on the available studies related to immunity and related areas. There is evidence that exposure of immune relevant cells such as macrophages/monocytes and dendritic cells to ELF-MF at different flux densities results in immune cell activation. The evidence from in vivo and in vitro studies suggest that short-term MF-exposure causes mild oxidative stress (modest reactive oxygen species (ROS) increases and changes in antioxidant levels) and possibly activates anti-inflammatory processes (decrease in pro-inflammatory and increase in anti-inflammatory cytokines). The few studies that specifically have investigated NDDs or NDD relevant end-points show that effects of exposure are either lacking or indicating positive effects on neuronal viability and differentiation. In both immune and NDD relevant studies, experiments with realistic long-term exposures are lacking, and consequences of a possible long-lasting mild oxidative stress are not investigated. Furthermore, the heterogeneity of the performed studies regarding physical, biological, and experimental parameters (e.g. exposure duration, the flux density, the biological endpoint and the cell type and the time point of investigation) is substantial and makes conclusions impossible. However, regarding immunity relevance it can be concluded:

- ELF-MF activates macrophages/monocytes via the alternative pathway to produce a mild rise of ROS and thus to alter the redox status,
- The changes in the intracellular redox status leads to modulation of ROS/antioxidant production, which in turn can induce an amplification of the immune response,
- The change in the redox homeostasis can further induce multiple mechanisms simultaneously, such as induction of different signal transduction pathways leading to the activation of secondary effects.

In summary, the existing experimental studies are not adequate in answering if there is a causal relationship between MF-exposure and NDD, since there is a lack of sufficient experimental studies. The notion that there is a connection between MF-induced ROS production and the development of NDD is rather implausible since relevant studies support anti-inflammatory responses to MF with positive rather than pathologic consequences.

Contact: Myrtill Simkó | myrtill.simko@sciproof-international.se

Session 8: Molecular responses to low frequency magnetic field exposure in cellular and animal models

Potential effect of low-frequency magnetic fields (LF-MFs) on mouse models of amyotrophic lateral sclerosis and Alzheimer's disease

Albrecht M. Clement | Institute for Pathobiochemistry, University Medical Center, Johannes Gutenberg University Mainz, Germany

Amyotrophic lateral sclerosis (ALS) and Alzheimer's dementia (AD) are devastating neurodegenerative diseases affecting different sets of neuronal populations. Although some ALS and AD cases are inherited, the vast majority of cases are sporadic. Therefore, environmental factors are discussed as potential risk factors. Several epidemiological studies investigated whether occupational and residential exposure to low-frequency magnetic fields (LF-MFs) increases the risk to develop ALS or AD. LF-MFs are generated by electrical current flow and can penetrate biological tissue. Some of these studies found a positive correlation between LF-MF exposure and disease.

To investigate whether LF-MFs interfere with molecular pathways involved in ALS and AD, we exposed transgenic mice expressing mutant SOD1 [SOD1(G85R) and SOD1(G93A) lines] and mutant APP (APP23 line), representing mouse models for ALS and AD, respectively, with constant LF-MFs (50 Hz, 1 mT) and compared them with sham-exposed animals. Exposure for 16 months did not alter total APP levels, nor were levels of soluble A (40) and A (42) increased. In line with these data, we did not observe an altered presence of A -plaques in exposed animals. Behavioral analysis revealed that long-lasting exposure with LF-MFs did not aggravate learning deficit of APP23 mice. Likewise, LF-MF exposure for ten or eight months did not alter disease onset and survival of SOD1(G85R) or SOD1(G93A) mice, respectively. These results and an extended biochemical analysis of protein aggregation, glial activation and levels of toxic protein species suggests that a continuous exposure with LF-MF is not sufficient to affect cellular processes involved in the pathogenesis of AD or ALS in established mouse models.

Contact: Albrecht M. Clement | clement@uni-mainz.de

Session 8: Molecular responses to low frequency magnetic field exposure in cellular and animal models

ELF-EMF and in vitro and non-transgenic in vivo models of neurodegenerative diseases

Isabelle Lagroye | Paris Sciences et Lettres Research University, University of Bordeaux, France

Neurodegenerative diseases (NDD) comprise both hereditary and sporadic conditions characterized by the progressive degeneration of the structure and function of the central nervous system or peripheral nervous system. The majority are of non-familial etiology and environmental factors and lifestyle play key roles in their pathogenesis. Extremely low-frequency electromagnetic fields (ELF MFs) are ubiquitously present at low exposure level in various environments of everyday life and at high exposure level in some specific occupational environments. Epidemiological studies (Huss et al, 2009; Frei et al. 2013) have provided controversial information about a possible association between residential exposure to ELF MFs of elderly people and Alzheimer disease (AD). Occupational exposures to 50/60 Hz magnetic fields have been associated with AD and Amyotrophic Lateral Sclerosis (ALS), although a recent meta-analysis concluded that overall the association was weak (Vergara et al. 2013).

Most experimental research dealing with the effects of ELF-MF has used rodent models for NDD, such as SOD-1 mouse models of ALS and different mouse models for AD (APP23, 3xTg, etc).
As mentioned above, because the majority of NDD are of non-familial etiology, non-genetic models of NDD have also been used in vitro and in vivo.

A cell model of Parkinson disease (PD), the MPP+ treated SH-SY5Y neuroblastoma cells suggested that ELF-MF could potentiate the effect of MPP+ by increasing ROS production, carbonyl proteins and apoptosis induced by the toxin (Benassi et al. 2016). However, there is so far no suggested epidemiological association between ELF-MF exposure and PD.

In the recent years, two AD rat models were published to investigate the effects of ELF-MF: (i) oral aluminum (Al) uptake and (ii) a combination of daily D-galactose injections and an acute injection of Aβ25–35 in the rat hippocampus. The results suggested that (i) ELF-MF exposure could not influence the pathogenesis of AD induced by Al overload (Zhang et al. 2013), and (ii) ELF-MF exposure could partially improve the spatial learning and the pathological damages in the brain of AD rats (Liu et al. 2015).

Other papers also suggested that ELF-MF exposure could improve the behavior of rats administered with 3-nitropropionic acid, a Huntington's disease-like rat model, at least in part through an anti-oxidant effect (Tasset et al, 2012; Tasset et al., 2013).

Overall, in vivo studies using non-genetic rodent models do not support the idea that ELF-MF could be a risk factor of AD and ALS. However, in those studies, young adult rodents were used and exposure duration was between 8 and 12 weeks. Whether the use of elderly animals and/or longer exposures would change the outcome is still to be determined.

Contact: Isabelle Lagroye | isabelle.lagroye@ims-bordeaux.fr

Session 8: Molecular responses to low frequency magnetic field exposure in cellular and animal models

Genetic damage following ELF-MF-Exposure in vitro: Relation with alzheimer's disease

Verschaeve L., Maes A., Anthonissen R. | Toxicology Unit, Scientific Institute of Public Health, Belgium

According to some studies exposure to extreme low frequency magnetic fields might be responsible for an increased risk of neurological disorders, including Alzheimer's disease. This was for example clearly indicated in the 2009 SCENIHR report stressing the need for further epidemiological and laboratory investigations. In their more recent 2015 report SCENIHR indicates that "Although the new studies in some cases have methodological weaknesses, they do not provide support for the previous conclusion that ELF MF exposure increases the risk for Alzheimer´s disease". It is thus far from clear whether Alzheimer's disease may or may not be associated with EMF-exposure. The issue is still under investigation.

Alzheimer's disease is, amongst others, characterized by the presence of amyloid β plaques between neural cells and the presence of phosphorylated TAU protein within the cells. Increased amyloid β synthesis was also found in a study on EMF-exposed animals. Alzheimer disease patients have also increased (cyto)genetic damage in their cells, as for example increased frequencies of micronuclei and trisomic cells, especially involving chromosomes 21 and 17 (resp. bearing the gene for amyloid β and tau protein). There is evidence for gene amplification and cell division disturbances in their cells.

We conducted an in vitro cytogenetic investigation on different human cell lines following a 24h exposure to ELF-magnetic fields. We found increased frequencies of structural and numerical chromosome aberrations (nucleoplasmic bridges and micronuclei) and gene amplification (nuclear buds) in cells that were exposed to >100 ↔T magnetic fields. This is in accordance with the scientific literature where increased chromosome aberration levels were reported at this and higher but not at lower exposure levels. However, 50↔T magnetic fields also significantly increased the frequency of nuclear buds (gene amplification). This is as far as we know a new finding. That micronuclei were predominantly large in size may also indicate that they were mainly the result of aneuploidy rather than a clastogenic event). We thus found genetic changes in magnetic field exposed cells (e.g., human C3A cells) that are in accordance with what is found in cells from Alzheimer disease patients. The exposure levels were however rather high and do not correspond to 'normal' low level exposure levels.

Exposure levels lower than 10 ↔T were also found to induce less than background levels of DNA damage and may as such indicate the presence of a DNA protection mechanism rather than an adverse effect. Literature data also indicated early activation of the immune system following very low EMF exposures. We therefore think that a short low level exposure to magnetic fields may prematurely activate the immune system and DNA repair mechanisms as part

of an adaptive response. However, there are limited indications that prolonged exposure initially lead to stimulation of the immune system but that this afterwards decreases (exhaustion?). Other limited data however contradicts this and hence this is worthwhile being further investigated.

Contact: Luc Verschaeve | luc.verschaeve@wiv-isp.be

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Kontakt:
Bundesamt für Strahlenschutz
Postfach 10 01 49
38201 Salzgitter
Telefon: + 49 30 18333 – 0
Telefax: + 49 30 18333 – 1885
Internet: www.bfs.de
E-Mail: ePost@bfs.de
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