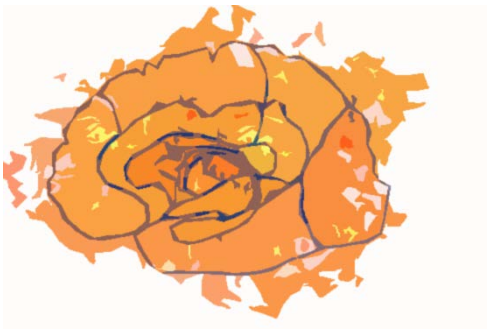

The aged brain in flames

Inflammatory events and brain function in the aged individual

Registration deadline: August 28th

Registration via agedbraininflames@gmail.com

Inflammation and pro-inflammatory cytokines are critical contributors to the onset and advancement of cognitive decline and mental dysfunction in frail elderly patients. |
How do inflammatory processes contribute to cognitive and mental dysfunction? What determines an individual's vulnerability to these processes? And how can we prevent or treat cognitive dysfunction in the elderly? These questions will be addressed in the mini-symposium "The aged brain in flames".
This symposium is organized by the department of Surgery (UMCG) and the department of Neurobiology (University of Groningen) and precedes the thesis defense "Characterizing postoperative cognitive dysfunction in the elderly" of Iris B Hovens.

Program

Wednesday September 9th
Rode zaal, UMCG, Hanzeplein 1, Groningen
9.30-10.00: Coffee
10.00-10.05: Opening by Prof Erik Buskens
10.05-10.35: Prof Erik Boddeke
10.35-11.05: Dr. Ruth Barrientos
11.05-11.30: Prof Chrystopher Pryce
11.30-11.55: Iris Hovens
11.55-12.25: Lunch
12.25-12.55: Dr. Aletta Kraneveld
12.55-13.20: Dr. Willem Bossers
13.20-13.30: Closure
13.30-14.30: Coffee

Erik H.W.G.M. Boddeke

Microglia and age-related neuroinflammation

H.W.G.M. Boddeke[1], I. Holtman[1], D. Raj[1], N. Brouwer[1], J.D. Laman[1], P. De Deyn[2], Z. Yin[1], B.J.L. Eggen[1]

[1]Department of Neuroscience, section Medical Physiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [2]Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Brain aging is associated with neurodegeneration and increased neuroinflammation of the central nervous system (CNS). Clearly, many signaling pathways are involved in age-related neuroinflammation and increasing evidence suggests that changes in microglia cells contribute to the age-related deterioration of the CNS. The most prominent age-related change of microglia is enhanced sensitivity to inflammatory stimuli, generally referred to as *priming. In microglia that were acutely isolated from mouse models for aging and* neurodegenerative disease we have identified specific gene networks and 'hub genes' for age-related neuroinflammation and microglia priming.
In APP23 mice expression of specific protein markers for microglia priming, including Mac-2, MHC-II and CD68, was observed specifically in plaque-associated microglia. An enhanced proinflammatory response to peripheral administration of LPS was observed only in plaque-associated microglia. Microglia outside the plaque areas did not express priming markers and showed only a moderate proinflammatory response to LPS. Similar enhanced expression of microglia priming markers and enhanced proinflammatory responses were observed in plaque-associated microglia in APP/PS1 mice and 5xFAD mice. In post-mortem brain samples of AD patients a similar expression of priming markers and enhanced expression of proinflammatory cytokines with plaque-associated microglia was observed. This was particularly evident in post-mortem brain tissue of juvenile AD patients where in absence of age-related microglia priming only priming and enhanced inflammation was observed in plaque-dense regions.

Ruth M. Barrientos (PhD)

Post-operative cognitive decline exacerbated by morphine treatment in aged rats

Department of Psychology & Neuroscience, and Center for Neuroscience, University of Colorado Boulder, Boulder, CO 90309, USA

Post-operative cognitive decline (POCD) refers to the constellation of cognitive changes ranging from feeling disoriented to having difficulty remembering events or sustaining attention, to dementia experienced most markedly by aged patients shortly following a surgical procedure. Laparotomy (an exploratory abdominal surgery) produces a potentiated inflammatory response in the hippocampus, and long-term memory impairments lasting 4 (but not 12) days post-surgery in aged, but not young adult rats. Clinical evidence suggests

that longer lasting POCD in humans leads to more severe outcomes such as dementia. Therefore, to develop and study a more clinically relevant model of POCD, we are currently examining the postoperative administration of morphine, as it is the gold standard for management of postoperative pain, and its chronic administration is known to induce robust neuroinflammation in rats via its activation of Toll-Like Receptor 4. Our findings demonstrate that aged rats that underwent surgery and received a 7-day course of morphine exhibited a) a significant decline in contextual memory and b) increased expression of proinflammatory cytokines (IL-1, IL-6, TNF-alpha) in the hippocampus 2 weeks post-surgery compared to rats that received laparotomy or morphine treatment alone. These effects were specific to aged rats, as young adult rats were not affected at this time point. Furthermore, these detrimental effects were still present in the aged rats 4 weeks post-surgery. These data suggest that chronic postoperative morphine treatment may cause profound memory declines in aged populations.

Christopher Pryce

Evidence from mouse models for the importance of tumor necrosis factor in the regulation of sickness and specific behavioural processes

Department of Psychiatry, University of Zurich, Zurich, Switzerland

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that is increased in infection, autoimmune disorders, and psychiatric disorders including depression. Animal studies are essential to increase understanding of the causal roles of TNF in aetio-pathophysiological pathways underlying sickness behaviour and specific behavioural processes. Brain region-specific chronic increases in viral-vector TNF resulted in increased fear conditioning in the absence of sickness, and peripheral TNF increased fear conditioning and decreased interest in reward in the absence of sickness. In a CD40 agonist antibody of autoimmune disease, sickness and decreased interest in reward were dependent on increased peripheral TNF. In an EAE model of multiple sclerosis, mice exhibited decreased fear conditioning dependent on increased hippocampal TNF and intact astrocyte TNF receptor 1 expression. Therefore, supra-physiological TNF levels contribute to sickness and sickness-independent behavioural processes, with the specific effects dependent on the overall status of the immune-inflammatory system.

Iris B. Hovens

Characterizing POCD in the Elderly

Department of Molecular Neurobiology, GELIFES & department of Surgery and Surgical Oncology, University of Groningen, Groningen, The Netherlands

An estimated ten percent of older surgical patients develops long-lasting postoperative cognitive dysfunction (POCD), associated with a reduced quality of life, increased dependency and worse prognosis. A good understanding of the characteristics and underlying mechanisms of POCD is essential to develop adequate (preventive) therapies. However, while patient studies have usually defined POCD as a persisting cognitive decline in general, mechanistic studies in animals have mainly focused on surgery-induced impairment in one brain region, the hippocampus.
We hypothesized that surgery-induced neuroinflammation disturbs sensitive brain areas of vulnerable patients, resulting in dysfunction in specific cognitive domains. To test this hypothesis, an unique rat-model for POCD was developed to study the influence of surgery on multiple brain regions and cognitive domains. This presentation provides a short overview of our research with this model characterizing postoperative cognitive performance and microglial activation as marker for neuroinflammation in rats with a low and elevated risk for POCD.

Aletta D. Kraneveld (PhD)

To be anounced

Willem J.R. Bossers (PhD)

Exercise is medicine

Center for movement sciences, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

A higher age (65+ years) often leads to a decline in so-called cognitive (thinking processes) and physical abilities (muscle strength, balance, and endurance). Such declines are accelerated when a person develops dementia. As a consequence, activities of daily living

(ADL) may be hampered and people become increasingly dependent on care. With the recent recognition that '*exercise is medicine*', physical exercise is suggested to be an effective non-pharmacological alternative to prevent the loss of cognitive and physical abilities.

In this lecture I will present the development of a nine-week-long exercise program in older patients with dementia and discuss the cognitive, physical, and ADL effects, and the hypothesized underlying mechanisms. In short, the results showed that a combined walking + strength training program led to better cognitive and motor functions than a walking-only program. These improvements transferred to improved ADL. However, nine weeks after the exercise program was completed, most of the cognitive and motor effects disappeared. Finally, I will shortly introduce future research, which focusses on the doses-response relationship and the underlying mechanisms of physical (in)activity on cognition.