Scotland in the Netherlands 2004

Brain Science Event
at The Royal Netherlands Academy of Arts and Sciences, Amsterdam

The Royal Society of Edinburgh

Royal Netherlands Academy of Arts and Sciences
Koninklijke Nederlandse Akademie van Wetenschappen

SCOTTISH EXECUTIVE

THURSDAY 30 SEPTEMBER

18:30 Doors open / Registration

19:00 Welcome by Professor Wiljan van den Akker,
Director of the Humanities and Social Sciences Institutes, KNAW

19:05 Public Lecture by Professor Richard Morris FRS, FRSE,
University of Edinburgh on ***How Brain Science could transform our lives in the 21st century***

Chair: Professor Peter Hagoort, FC Donders Centre
for Cognitive Neuroimaging, Nijmegen

20:10 – 21:00 Reception hosted by Sir Colin Budd KCMG, British Ambassador,

and exhibition on brain science in the UK and the Netherlands

FRIDAY 1 OCTOBER

08:45 Registration

09:00 – 09:05 Welcome by Professor Willem Levelt – President of KNAW

09:05 – 10:35 Session 1 – ***Language***. Chair: Professor Willem Levelt, President of KNAW;
Rapporteur: Dr Doug Davidson, FC Donders Centre & Max Planck Institute, Nijmegen

a Professor Simon Garrod FRSE, University of Glasgow
Why is conversation so easy?

b Professor Peter Hagoort, FC Donders Centre for Cognitive Neuroimaging, Nijmegen
On broca, brain and binding

c Dr Ardi Roelofs, Max Planck Institute for Psycholinguistics, Nijmegen
The language user as Ben-Hur: Modelling the hemodynamics of control

d Professor Johanna Moore FRSE, University of Edinburgh
Generating user-adapted descriptions in spoken dialogue

10:40 –11:00 Coffee / Refreshments

11:00 –11:45 Panel Discussion –
Professor Anne Anderson OBE, University of Glasgow;
Professor Gerard Kempen, Leiden University;
Professor Mark Steedman, FBA FRSE, University of Edinburgh

11:45 –12:30	Session 2 – ***Memory and Cognition***. Chair: Professor Richard Morris FRS, FRSE; Rapporteurs: Dr David Donaldson, Dr Onno Meijer **a** Professor Robert Logie FRSE, University of Edinburgh *Working memory function and dysfunction in ageing and in Alzheimer's disease* **b** Dr Guillén Fernández, FC Donders Centre for Cognitive Neuroimaging, Nijmegen *Exploring the human declarative memory system by functional neuroimaging*
12:45 – 14:00	Lunch – includes time to meet with journalists and speech by Dr Mac Armstrong, Chief Medical Officer for Scotland
14:00 – 14:45	***Memory and Cognition*** (cont'd) **c** Dr Emma Wood, University of Edinburgh *Neural correlates of memory in the hippocampus* **d** Professor Cyriel Pennartz, University of Amsterdam *Reactivation in the brain: trying to track memory traces*
14:45 – 15:30	Panel Discussion – Dr David Donaldson, University of Stirling; Professor Jaap Murre, Maastricht University; Professor Keith Stenning, University of Edinburgh
15:30 – 16:00	Tea
16:00 – 17:30	Session 3 – **Stress**. Chair: Professor Ronald de Kloet, Leiden University; Rapporteur: Dr Megan Holmes **a** Professor Marian Joëls, University of Amsterdam *Stress and brain function* **b** Dr Fiona Thomson, Organon Pharmaceuticals, Scotland and NL *Innovative approaches for the treatment of depression: targeting stress and the HPA axis* **c** Professor Jonathan Seckl FRSE, University of Edinburgh *Stress, steroids and enzymes: a new approach to memory impairments in old age* **d** Professor Anton Schoffelmeer, Vrije Universiteit Amsterdam *Towards a pharmacotherapy of addiction*
17:30 – 18:15	Panel Discussion – Dr Megan Holmes, University of Edinburgh; Dr Onno Meijer, Leiden University; Dr Melly Oitzl, Leiden University
18:15	Session Chairs to report and Closing Remarks
18:30	Return to hotel. No formal programme.

SESSION 1 Language

Session Chair

Professor Willem Levelt, President of the Royal Netherlands Academy of Arts and Sciences

Biography: Willem Levelt is founding director of the Max Planck Institute for Psycholinguistics in Nijmegen, The Netherlands and Honorary Professor of Psycholinguistics at Radboud University Nijmegen. His books include *On binocular rivalry* (1965), *Formal grammars in Linguistics and Psycholinguistics* (3 Vols, 1974) and *Speaking: From intention to articulation* (1989). He is President of the Royal Netherlands Academy of Arts and Sciences and a member of various academies, among them the US National Academy of Sciences, The American Philosophical Society and the Academia Europaea.

Speakers

Why is conversation so easy?

Professor Simon Garrod FRSE, University of Glasgow

Traditional accounts of language processing suggest that monologue – preparing and listening to speeches – should be more straightforward than dialogue – holding a conversation. This is clearly not the case. I will argue that conversation is easy because of an interactive processing mechanism that leads to the alignment of linguistic representations between conversationalists. Interactive alignment occurs via automatic alignment channels which are functionally similar to the automatic perception – behaviour links (the so-called perception – behaviour expressway) proposed in recent accounts of social interaction. I conclude that humans are 'designed' for dialogue rather than monologue. This leaves the question of how the neural substrates of language processing are designed to take advantage of interactive alignment processes.

Biography: Simon Garrod is currently Professor of Cognitive Psychology at the University of Glasgow. Between 1989 and 1999 he was also Deputy Director of the ESRC Human Communication Research Centre. He has held visiting Fellowships at the Max Planck Institute for Psycholinguistics in Nijmegen and the Netherlands Institute for Advanced Study in Wassenaar. He has published two books, *Understanding written language* (with A.J. Sanford) and *Seeing, saying and acting: The psychological semantics of spatial prepositions* (with K. Coventry), as well as over a hundred research papers on various aspects of the psychology of language. His special interests include discourse processing, language processing in dialogue, psychological semantics and graphical communication. He is a Fellow of the Royal Society of Edinburgh.

On broca, brain and binding

Professor Peter Hagoort, FC Donders Centre for Cognitive Neuroimaging

This presentation will focus on the binding problem for language. That is, once lexical information has been retrieved from memory on the basis of acoustic (speech) or visual (reading) input patterns, single word information has to be unified into a coherent overall interpretation of the utterance.

This binding or unification requires that lexical information is maintained active over time while unification operations take place. I will argue that the left prefrontal cortex is neuronally well suited for this task. In addition, EEG/MEG and fMRI data will be discussed that support this hypothesis. In addition, the nature of these binding operations will be discussed.

Biography: Peter Hagoort is the founding director of the FC Donders Centre for Cognitive Neuroimaging (1999), a cognitive neuroscience research centre based at the Radboud University of Nijmegen, with the participation of the Universities of Maastricht, Utrecht and Tilburg, and the Max Planck Institute for Psycholinguistics. Since 1990 he has led the research group “Neurocognition of Language Processing” at the Max Planck Institute for Psycholinguistics, in Nijmegen. He is Professor in Cognitive Neuroscience at the Radboud University Nijmegen, and University Affiliate of the Max Planck Institute for Psycholinguistics. His own research interests relate to the domain of the human language faculty and how it is instantiated in the brain. In his research he applies neuroimaging techniques such as ERP, MEG, PET and fMRI to investigate the language system and its impairments as in aphasia and dyslexia. At the FC Donders Centre he is heading the research group Neurocognition of Language (6 postdocs, 8 PhDs). For his scientific contributions, the Royal Netherlands Academy of Arts and Sciences (KNAW) awarded him with the prestigious Dr Hendrik Muller Prize for Behavioural and Social Sciences in 2003. Peter Hagoort is a Fellow of the KNAW.

The language user as Ben-Hur: modelling the hemodynamics of control

Dr Ardi Roelofs, Max Planck Institute for Psycholinguistics, FC Donders Centre for Cognitive Neuroimaging, Nijmegen Institute for Cognition and Information

Cognitive control, the ability to formulate goals and plans of action and to follow these in the face of distraction, is a hallmark of verbal and nonverbal intelligence. The issue of cognitive control was exemplified by Plato in Phaedrus as the problem of a charioteer trying to manage horses pulling in different directions. The anterior cingulate cortex (ACC), on the medial surface of the frontal lobes of the human brain, is widely believed to be involved in cognitive control. Previous functional neuroimaging studies showed that the presence of conflicting response alternatives yields an increase in ACC activity. The prevailing view of ACC function maintains that the increased activity reflects the detection of response conflict. ACC activity acts as a signal that engages executive control processes in lateral prefrontal areas. However, the increased activity is also compatible with the view that the ACC plays a role in executing control itself. We obtained evidence that adjudicates clearly between the two views. Subjects responded to incongruent, congruent, and neutral arrow-word combinations in an event-related functional magnetic resonance imaging (fMRI) experiment. ACC activity was higher on neutral than on congruent trials in the absence of conflicting response alternatives, demonstrating engagement of the ACC in aspects of performance unrelated to response conflict *per se*. Computer simulations showed that the GRAIN model, which implements ACC conflict detection, does not account for the findings, whereas the WEAVER++ model, which implements ACC executive control, does.

Biography: Ardi Roelofs is senior staff member of the Max Planck Institute for Psycholinguistics, Research Fellow of the FC Donders Centre for Cognitive Neuroimaging, and senior researcher at the Nijmegen Institute for Cognition and Information. He obtained his BA, MA, and PhD degrees (all *cum laude*) in psychology from Radboud Nijmegen University. After a postdoctoral year in the Department of Brain and Cognitive Sciences at MIT, in Cambridge, USA (1992–1993), he was staff member at the Max Planck Institute for Psycholinguistics in Nijmegen (1993–1998) and Lecturer in Psychology and Reader in Cognitive Science at Exeter University in England (1998–2001). In 2003, he obtained a prestigious NWO Vici grant for the project "Goal-referenced control of verbal and nonverbal action", which allowed him to establish his own research group at Radboud Nijmegen University. The group uses chronometric, eye tracking, electrophysiological, functional neuroimaging, and computational modelling techniques to study cognitive control.

Generating user-adapted descriptions in spoken dialogue

Professor Johanna Moore FRSE, University of Edinburgh

When people engage in conversation, they adapt to their conversational partner in many aspects of language use, including speaking rate and response delay, amplitude and prosodic range, lexical and syntactic choice, and higher level discourse processes such as the selection of content and form for persuasive arguments and negotiation. Such adaptation has been shown to improve listeners' comprehension, the efficiency with which they execute conversational tasks, and the likelihood of achieving higher level goals. In this talk, I describe algorithms that enable dialogue systems to generate recommendations and comparisons that are adapted to the preferences and constraints of the current user. This work brings together multi-attribute decision models for user modelling, strategic content planning, and a realisation component, OpenCCG, that uses information structure to control prosodic features during speech synthesis. This talk emphasizes how the user model influences virtually every aspect of the generation process, including selection of the most important subset of available options to mention and the attributes that are most relevant to choosing between them; organization of the selected content; expression of descriptions of selected options and attributes; and selection of international features.

Biography: Johanna D. Moore is Professor of Artificial Intelligence at the University of Edinburgh, and Director of the Human Communication Research Centre. From 1990 to 1998, she was Assistant, then Associate Professor of Computer Science at the University of Pittsburgh, where she held a joint appointment as a Research Scientist in the Learning Research and Development Center. From 1996 to 1998, she was director of the interdisciplinary PhD program in Intelligent Systems at the University of Pittsburgh.

Professor Moore has directed and participated in numerous externally funded research projects in both the United States and in Europe, in which she applies her expertise in natural language processing, dialogue and discourse, planning, and knowledge representation to problems in spoken dialogue systems, customised information presentation, intelligent tutoring systems, and multimodal interaction.

Professor Moore is the President of the Association for Computational Linguistics, a member of the Governing Board of the Cognitive Science Society, and a Fellow of the Royal Society of Edinburgh. She has served as Associate Editor of the *Journal of Artificial Intelligence Research*, Guest Editor for the journals *Computational Linguistics* and *Knowledge Based Systems*, and on the editorial board of several major journals in the field. She has been on program committees for major conferences in computational linguistics, artificial intelligence, human-computer interaction, and computers and education. She has served as Program Chair for the Cognitive Science Conference and the World Conference on Artificial Intelligence and Education, and co-Conference Chair of the International Conference on Intelligent User Interfaces.

Discussants

Biography: **Professor Anne Anderson OBE**, University of Glasgow is a psychologist interested in human communication and the impacts of new information and communication technologies. Her research over several years has investigated how people communicate and collaborate. She has been particularly concerned with understanding dialogue and the role of visual and verbal signals in interaction. In her research she has also investigated the impact of new technologies such as multimedia communication systems on their users. She has held many research grants on these topics funded by the Economic and Social Research Council (ESRC), the Engineering and Physical Sciences Research Council (EPSRC), the EC and industry. She has published widely on the psychology of human communication and computer-supported collaborative working.

Professor Anderson was a Principal Investigator in the Human Communication Research Centre funded from 1990 to 2000 by ESRC. She has held a chair in psychology since 1997 at the University of Glasgow where she runs the Multimedia Communications Laboratory in the Department of Psychology. The department was awarded the highest grade, a 5*, in the recent Research Assessment Exercise. From 1995 to 2000 she was director of the ESRC Cognitive Engineering programme, an initiative which funded 15 projects across the UK on topics concerned with people and information technology. In 2000 she was appointed Director of the People at the Centre of Information and Communication Technologies (PACCIT) programme. This is a £8 million LINK programme funded by ESRC, EPSRC, and the DTI and seeks to build research collaborations between the universities and industry. In 2002 she was awarded an OBE for services to social science.

Biography: **Professor Gerard Kempen** (1943), Leiden University, has been Professor of Cognitive Psychology since 1992, and Research Associate of the Max Planck Institute for Psycholinguistics in Nijmegen since 1999. From 1976 to 1992 he was Professor of Psycholinguistics at the University of Nijmegen, where he had received his PhD in 1970. His scientific work concerns the grammatical aspects of human sentence production and comprehension. He is studying these topics through a combination of linguistic, experimental-psychological and (neuro-) computational methods. His contributions include the lemma-lexeme distinction and the concept of incrementality in language production, the Unification-Space Parser (with Theo Vosse), and the psychologically motivated Performance Grammar formalism (with Koenraad De Smedt and Karin Harbusch). Since 1980 he has initiated and supervised various theoretical and applied research projects dealing with the computational treatment of Dutch, among other things, for visual-interactive grammar instruction.

Biography: **Professor Mark Steedman FBA, FRSE**, University of Edinburgh, graduated in Experimental Psychology from the University of Sussex in 1968 and gained his PhD in Artificial Intelligence from the University of Edinburgh in 1973.

Currently, he is Professor of Cognitive Science and Director of the Institute for Communicating and Collaborative Systems in the School of Informatics at the University of Edinburgh, and Adjunct Professor in Computer and Information Science at the University of Pennsylvania. Previously, he was Professor (1992–1998) and Associate Professor (1988–1992) in Computer and Information Science at the University of Pennsylvania.

He has published widely in international journals and is the author of two books, *Surface Structure and Interpretation* (1996), and *The Syntactic Process* (2000).

He is a Fellow of the American Association for Artificial Intelligence, the Royal Society of Edinburgh and the British Academy.

SESSION 2
Memory and Cognition

Session Chair

Professor Richard Morris FRS, FRSE, University of Edinburgh

Biography: Richard Morris has been Professor of Neuroscience at the University of Edinburgh since 1993. In 1969 he graduated with a MA from Natural Sciences at the University of Cambridge and in 1973 he completed a DPhil at the Laboratory of Experimental Psychology of the University of Sussex.

His primary research interests are the neurobiology of learning and memory, and the applications of concepts and techniques developed in this work to help develop new therapeutics for Alzheimer's Disease.

Morris invented and developed the 'watermaze' as a method to study spatial learning (Morris *et al*, *Nature*, 1982), discovered the role of NMDA receptors in learning (Morris *et al, Nature*, 1986), and developed the synaptic tagging theory of the persistence of memory (Frey and Morris, *Nature*, 1997). Professor Morris serves as an advisor for a number of international research institutes, is a member of the Scientific Advisory Board of the Alzheimer's Research Trust in the UK, the Scottish Science Advisory Committee, and he is President-Elect of the Federation of European Neuroscience Societies (FENS). He is also an active member of the Council of the European Dana Alliance for the Brain, whose mission is public awareness of neuroscience.

Speakers

Working memory function and dysfunction in ageing and in Alzheimer's disease

Professor Robert Logie FRSE, University of Edinburgh

The average age of the population of Western Europe is increasing to the extent that within a decade, people of retirement age may well be in the majority. With this will come an increase in the number of people suffering from cognitive changes with age, and as sequellae to the dementias. Cognitive Neuroscience has, and will have, a crucial role to play in developing an understanding of these cognitive changes to assist with early detection, with evaluation of therapies, and with the management of cognitive impairments to extend independent living. The societal importance is complemented by the scientific importance of understanding the links between cognitive function and brain organisation, using a combination of behavioural experimental techniques and methods for exploring the neuroanatomical correlates of cognitive operations.

This paper will first review research examining the changes in cognitive functions that are associated with old age and with the early stages of Alzheimer's Disease (AD), set in the context of working memory. The discussion then will focus on recent research showing how the ability to perform two tasks concurrently is specifically impaired in Alzheimer's patients while being less evident in healthy ageing. The different dual task effects on memory are more prevalent during memory encoding than during retrieval. However performance on a secondary, response time task seems to be more affected during the retrieval phase of a concurrent memory task. Overall demands of the secondary response time task had fairly subtle effects, suggesting that it is dual task demands that are crucial rather than overall task demand. Results will be interpreted as indicating a dual task co-ordination function within the healthy brain that shows a specific deterioration in AD. Implications for detection and management of the cognitive impairments observed will be discussed.

Biography: Robert H. Logie completed his first degree in Psychology at the University of Aberdeen, and his PhD at University College, University of London. Subsequently (1980 – 86), he worked at the Medical Research Council Applied Psychology Research Unit in Cambridge. In 1987 he took up a lecturing post in Psychology at the University of Aberdeen, UK, becoming Anderson Professor and Head of Department 1997 – 2003. In January 2004 he was appointed as Professor of Human Cognitive Neuroscience at the University of Edinburgh, UK, and since 1996 has been Adjunct Professor of Cognitive Psychology at the University of Bergen, Norway. He is a Fellow of the Royal Society of Edinburgh, of the Royal Society of Arts, of the British Psychological Society, and an Academician of the Academy of Learned Societies in the Social Sciences. He is Editor of *The Quarterly Journal of Experimental Psychology* (A), and is author of over 80 peer reviewed scientific articles, three authored books, ten edited books, and over 30 scientific book chapters. His research, publications and grants cover theoretical and applied cognitive psychology, cognitive neuropsychology, human factors and ergonomics, with projects ranging from memory and attention deficits associated with focal brain damage and with Alzheimer's disease, through visual creative thinking, to the design of computerized patient monitoring and medical decision support systems in intensive care.

Exploring the human declarative memory system by functional neuroimaging

Dr Guillén Fernández, FC Donders Centre for Cognitive Neuroimaging

The kind of memory one ordinarily means when using the term memory is declarative memory, which enables us to retrieve consciously past events and facts. After an era when lesion studies have identified the declarative memory system and its essential anatomical structures, functional imaging techniques such as functional MRI and electrophysiology have begun to delineate the neural underpinnings of mnemonic operations, such as the formation of new memories and the retrieval of old ones. Here, I will initially characterize the neural correlates of these transient and short-lasting operations occurring during memory encoding and retrieval. Thereafter, I will present new data shedding some light on declarative memory consolidation, a presumably long lasting (set of) operation(s) transforming initial, unstable memory traces into stable forms of long-term memory. Our functional MRI data seem to provide initial confirmation for the time limited role of the hippocampus in human declarative memory. With time, memory retrieval is associated with less and less hippocampal activity but in turn with more and more activity in neocortical brain areas related to the specific cortical representation of the stimuli. Moreover, our data is in line with the notion that slow-wave- and rapid-eye-movement in sleep play a crucial role in this operation. In conclusion, functional imaging provides a useful tool for assessing the neural correlates of fundamental mnemonic operations. Thus, we might use these techniques in the near future to probe the genetic and biochemical basis of the normal and the impaired declarative memory system.

Biography: Dr Guillén Fernández graduated in Medicine in 1994 and in Neurology in 2000. Since then he has worked as a physician and furthered his research career in different universities including Bonn, Magdeburg and Stanford.

In 2002, he received the Richard-Jung-Award from the German Society for Clinical Neurophysiology and Functional Imaging. He is currently Principal Investigator at the FC Donders Centre for Cognitive Neuroimaging in Nijmegen.

He is widely published in international journals himself as well as being a referee for journals and funding organisations. He has more than ten grants and scholarships which include grants from DFG (German Research Council), NWO (Dutch Organisation for Scientific Research) and the Volkswagenstiftung.

Neural correlates of memory in the hippocampus

Dr Emma Wood, University of Edinburgh

The hippocampal formation of the medial temporal lobe has long been implicated in memory, most notably in spatial memory and in episodic memory for specific autobiographical events. For example, amnesic patients with damage restricted to the hippocampus suffer from impaired spatial and episodic memory, and functional imaging studies in control subjects show hippocampal activation during spatial and episodic memory tasks. By recording from individual hippocampal neurons in awake, behaving animals, it is possible to examine the relationship between hippocampal neuronal activity and behaviour. Such single-unit recording studies have revealed the existence of hippocampal place cells that have strong spatially localised firing. In this talk I will describe our experiments investigating how hippocampal place cells may contribute to spatial memory and also how they may provide the building blocks for certain aspects of episodic memory, including memory for sequences of events, and for non-spatial stimuli. This research is supported by the BBSRC.

Biography: After obtaining a BSc in Psychology from the University of St Andrews in 1987, Emma Wood went to the University of British Columbia to study for a PhD in Neuroscience (1987–1992). There she worked with her supervisor, Professor Anthony Phillips, on ischemia-and lesion-induced models of medial temporal lobe amnesia in rats. Her initial postdoctoral research was carried out at the Institute of Neuroscience, University of Oregon (1993–95), where she studied neural mechanisms of learning in the insect *Manduca sexta* with Professor Janis Weeks. She then moved to the Department of Psychology, Boston University (1996–99), where she worked with Professor Howard Eichenbaum on the role of the mammalian hippocampus in memory, using single-unit electrophysiological recording techniques. She joined the University of Edinburgh in 1999 as a Lecturer in Neuroscience, and there has been continuing her investigation into the role of the hippocampus in memory. This uses an integrated approach to the problem, including multiple single-unit recording from awake, behaving rats, together with lesion, neuropharmacological, and behavioural techniques.

Reactivation in the brain: trying to track memory traces

Professor Cyriel Pennartz, University of Amsterdam

Memories are assumed to undergo a 'consolidation' phase, meaning that their storage in the brain is gradually strengthened and becomes more resistant against loss or damage. The process of declarative memory – the kind of memory we are conscious of and can report about – has been shown to depend on interactions between the hippocampus and neocortex, but we know very little about how consolidation might occur in these brain systems, and how they interact during memory formation. A clue for studying this became available when it was discovered that these structures can spontaneously 'reactivate' during sleep and rest periods that follow an important behavioural event. Especially in studies where the electrical activity of large numbers of neurons can be tracked during learning behaviour and sleep, it has become clear that such 'reactivation' may hold that brain activity patterns pertaining to learning episodes can be 'replayed' in an off-line phase of processing. We examined whether reactivation can also occur in a subcortical structure – the ventral striatum, which has been implicated in the expression of emotional behaviour as well as drug addiction. New technologies enabling us to perform parallel recordings from many brain cells simultaneously proved instrumental in showing that reactivation does indeed occur in the ventral striatum, and was associated with a specific type of mass activity related to reactivation in the hippocampus. These data suggest how brain structures may interact in the process of reactivation, and show that this process is not restricted to the dialogue between hippocampus and neocortex. The implications of this type of research for future treatment of anxiety, drug addiction and related neuropsychiatric conditions are discussed.

Biography: Cyriel Pennartz graduated in Neurobiology at the University of Amsterdam in 1987. Under the supervision of Fernando Lopes da Silva he conducted his PhD research on the physiological principles that govern nervous activity in a brain nucleus involved in addiction, emotion and motivation. After this period in experimental neuroscience, he worked as a postdoc with John Hopfield at Caltech on computational models of neural networks that learn by processing reward in addition to sensory and motor information. From 1994 to 2002 he held a staff position in Electrophysiology at the Netherlands Institute for Brain Research, investigating both the question as to how our prefrontal cortex is modified and used during learning, and how the brain's biological clock comes to produce a day-night cycle in its output, constituted by nervous impulses. In 2002 he became a Special Professor in Cognitive Neurobiology at the University of Amsterdam, and 2003 Full Professor in Animal Physiology and Cognitive Neuroscience. At this time his new group is being formed, including disciplines such as Cognitive Neurophysiology, Human Brain Imaging and Neurochemistry.

Discussants

Biography: **Dr David Donaldson**, University of Stirling is a Senior Lecturer in Psychology at the University of Stirling and Principal Investigator of the Psychological Imaging Laboratory. His research is focused around a simple question: how does human memory work? To investigate this question he uses behavioural and neuroimaging methods to identify and dissociate the cognitive processes underlying memory. Dr Donaldson gained a 1st Class BSc at the University of Manchester in 1994. He was then awarded a Wellcome Trust PhD Studentship in Event-Related Potentials and Human Memory, allowing him to study as a post graduate student at the University of St Andrews, where he gained his PhD in 1998. Dr Donaldson successfully applied for a prestigious Wellcome Trust International Travelling Research Fellowship, supporting a two-year post-doctoral post at Washington University in St Louis, using functional Magnetic Resonance Imaging to study memory. Dr Donaldson then returned to Scotland, starting as a Lecturer in Psychology in 2001, and becoming Senior Lecturer in 2004. He is extremely active as a researcher, from giving public lecturers on memory to arranging specialist workshops, and continues to develop the use of behavioural and neuroimaging techniques as a way of investigating human memory.

Biography: **Professor Jaap Murre**, Maastricht University, completed Master's degrees in Psychology and in Experimental Phonetics at the University of Utrecht, in 1987. In 1992, he received his PhD from Leiden University. From 1992 to 1995, he worked as a scientist at the Applied Psychology Unit of the Medical Research Council in Cambridge, UK. In 1995, he moved to the Psychology Department of the University of Amsterdam, where he worked as a research fellow sponsored by the Netherlands Royal Academy of Arts and Sciences (KNAW) until June 2000. From 1999 to 2004, he held a PIONIER grant from the Netherlands Organization for Scientific Research (NWO). Professor Murre holds a special chair in 'Neural Models of Cognition' at the Computer Science Department of the University of Maastricht and he is employed as an Associate Professor at the Psychology Department of the University of Amsterdam. His research interests centre around modelling human learning and memory, including their biological basis and pathology (see www.neuromod.org and www.memory.uva.nl).

Biography: **Professor Keith Stenning**, University of Edinburgh, is a cognitive scientist whose chief interest is the interplay of formal theory and psychological experiment in understanding human reasoning and communication. He read philosophy and psychology as an undergraduate at Oxford, followed by a PhD at Rockefeller University in New York. He was Director of the interdisciplinary Human Communication Research Centre in Edinburgh and Glasgow Universities.

A recent book is entitled *Seeing Reason: language and image in learning to think*. Other recent work with Michiel van Lambalgen of Amsterdam applies modern logical analyses of natural language semantics to reveal how psychologists have failed to communicate with their subjects in their experiments on reasoning. The subjects emerge as more rational but the experimenters somewhat less so. These analyses have direct consequences for the implementation of non-standard logics in the brain, and for the evolution of higher mental processes.

As Chair of the Cognitive Science Society 2002–3 he was instrumental in persuading that Society to internationalise its activities by holding regular conferences in Europe.

SESSION 3 Stress

Session Chair

Professor Ronald de Kloet, Leiden University

Biography: Professor de Kloet is Head of the Department of Medical Pharmacology (LACDR/LUMC) of Leiden University. His main interest is the neuroendocrinology of stress and ageing, and its relevance to stress-related psychiatric disorders, such as depression. He discovered two types of corticosteroid receptors in the brain that have a dual operation in stress system biology. One receptor type helps to organize the stress response, which is terminated via the other type, and their balance is crucial for health. De Kloet is on the Editorial Board of ten journals including *Endocrinology* and *Frontiers in Neuroendocinology*. He has been identified by ISIhighlycited.com as one of the most cited authors in the neurosciences, and he has published more than 450 articles. Recently he was awarded the Academy Professorship of the Royal Netherlands Academy of Arts and Sciences.

Speakers

Stress and brain function

Professor Marian Joëls, University of Amsterdam

Stressful situations activate the hypothalamus-pituitary-adrenal (HPA) system which leads to a rise in circulating corticosteroid levels (cortisol in humans, corticosterone in most rodents). These hormones can enter the brain and bind to two types of receptors, i.e. the mineralocorticoid and glucocorticoid receptors (MR and GR respectively), which are enriched in the hippocampal formation. Activated corticosteroid receptors function as transcriptional regulators of responsive genes. Recent studies employing various expression profiling techniques – ranging from extensive gene screening to investigation of specific sets of genes in single neurons – have shown that activation of GRs in addition to MRs, such as happens after a brief period of stress, modifies the expression of various genes in hippocampal neurons. One of the subunits encoding for the L-type voltage dependent calcium channel (VDCC) was consistently found to be upregulated by stress and/or GR activation. In agreement, currents carried by the L-type VDCC were slowly but persistently enhanced after stress. Under physiological conditions VDCCs play an important role in cellular homeostasis and cell function, including synaptic strengthening. We demonstrated that long-term potentiation requiring VDCC activation is indeed enhanced by GR activation, whereas other types of synaptic potentiation are diminished. This may signify that, depending on the circumstances and therefore on the type of synaptic potentiation that is induced, memory processes could be differentially affected by stress hormones. Pathological conditions leading to prolonged activation of VDCCs are exacerbated by stress and GR occupation.

Biography: Marian Joëls is Professor of Zoology at the Swammerdam Institute for Life Sciences, University of Amsterdam. She presently heads the Neurobiology Section of this Institute. The focus of her research is on the cellular effects of corticosteroid hormones in brain, in health and disease. This is mostly examined with electrophysiological techniques, ranging from single channel recordings to the monitoring of field potentials in freely moving animals. In combination with molecular, immunohistochemical, morphometric and behavioural approaches, the research group furthermore aims to understand the molecular mechanism underlying the cellular effects as well as their functional implications. Marian Joëls is a member of numerous committees and societies, including NWO, the graduate school Neuroscience Amsterdam and the KNAW.

Innovative approaches for the treatment of depression: targetting stress and the HPA axis

Dr Fiona Thomson, Organon Pharmaceuticals, Scotland and NL

Preclinical and clinical studies have provided substantial support for the hypothesis that alterations in the stress system play a critical role in the development of depression and anxiety disorders. There is growing opinion that chronic exposure to stressful life events, especially during early development, in combination with genetic susceptibility factors, can result in an individual developing depressive illness.

The hypothalamic pituitary adrenal (HPA) axis is the major system that is activated in response to a stressor. Hyperactivity of the HPA axis is the most consistently described neuroendocrine abnormality in severe depression. Irregularities include elevated serum and 24hr urinary cortisol, dysfunctional glucocorticoid receptor (GR)-mediated negative feedback regulation, adrenal gland hyperplasia, a blunted release of adrenocorticotrophin hormone (ACTH) in response to corticotrophin releasing hormone (CRH) and a shift towards a predominant arginine vasopressin (AVP) regulation of ACTH release. Observations that clinical remission is associated with normalisation of HPA axis activity has led to the hypothesis that drugs that target the overactive HPA axis could have benefit for the treatment of the symptoms of depression and anxiety disorders. Perhaps the most compelling evidence comes from clinical studies of GR antagonists, cortisol synthesis inhibitors and corticotrophin-releasing factor (CRF)-1 antagonists. All of these approaches have shown improvement in symptoms to some extent with the synthesis inhibitors also demonstrating treatment of patients with rapid onset of action.

Within our drug discovery programme, we have adopted a variety of therapeutic strategies for the treatment of psychiatric disorders that are based on intervention of the hyperactive stress axis. Based on evidence that HPA axis dysfunction may result from a combination of impaired glucocorticoid-mediated negative feedback and/or overdrive of the system by hypothalamic hormones such as AVP, we have been investigating the use of antagonists of the glucocorticoid and the vasopressin V1b receptors. The clinical and preclinical evidence supporting the use of such compounds for the treatment of psychiatric disorders shall be presented together with our ongoing strategy for identifying and validating novel drug targets for the treatment of diseases associated with stress axis dysfunction.

Biography: Fiona Thomson gained a BSc in Biological Sciences, before completing a PhD in Molecular Pharmacology at the University of Edinburgh in 1992. Her PhD studies were undertaken in the MRC Brain Metabolism Unit, under the supervision of Dr Rory Mitchell and Professor George Fink, where she investigated the intracellular signalling pathways of the GnRH receptor in regulation of gonadotrophin release. Continuing with this theme, her postdoctoral research has focused on the role of G-protein coupled receptors (GPCRs) in health and disease, initially at the Schering Plough Research Institute in the USA where she developed an interest in lysophosphatidic acid (LPA) receptors in inflammatory diseases. On her return to the UK in 1994, Fiona continued her research in the field of LPA receptors as a postdoctoral associate at the University of Glasgow and was subsequently awarded a Fellowship from the British Heart Foundation. Fiona joined Organon in 1997, where she now heads the Receptor Pharmacology Section in the Department of Molecular Pharmacology, Newhouse, Lanarkshire, Scotland. She also leads the preclinical CNS team that is responsible for Organon's early drug discovery research in psychiatric disorders. Her current research interests include investigating novel drug mechanisms, for the treatment of stress related disorders such as depression and anxiety, based on manipulation of the hypothalamic pituitary adrenal axis.

Stress, steroids and enzymes: a new approach to memory impairments in old age

Professor Jonathan Seckl FRSE, University of Edinburgh

Many intuitively believe that chronic stress is bad for body and brain. Indeed, long-term elevation of levels of glucocorticoid steroid hormones (cortisol, corticosterone), key components of the body's response to stress, adversely affect cognitive processes and the structural and functional integrity of the hippocampus. Crucially, inter-individual differences in memory with ageing directly associate with blood glucocorticoid levels in rodents and humans; higher glucocorticoid levels linking with subsequent memory impairments. However, although keeping glucocorticoid levels low by adrenalectomy in mid-life prevents the emergence of memory impairments with age in rats, such 'prophylactic surgery' is not a practical alternative in human therapy, not least because glucocorticoid deficiency is also harmful.

Recent data suggest that pre-receptor metabolism by enzymes called 11ß-hydroxysteroid dehydrogenases (11ß-HSDs), which interconvert active glucocorticoids and their inert 11-keto metabolites, potently regulates glucocorticoid action in specific cells *in vivo*, including in the brain. The brain highly expresses 11ß-HSD type 1. This isozyme is a reductase in intact neurons and glia, which functions to regenerate active steroids and thus locally amplifies glucocorticoid effects. Inhibition of 11ß-HSD1 protects hippocampal cells from neurotoxic challenge *in vitro*. Moreover, mice lacking 11ß-HSD1 resist the usual glucocorticoid-associated impairments of cognitive (hippocampal) function with ageing. 11ß-HSD1 is also expressed in the adult human CNS. The 11ß-HSD inhibitor carbenoxolone improves aspects of cognitive performance in elderly humans. 11ß-HSD1 may be a useful therapeutic target in age-related cognitive disorders and is a prototype for tissue-specific manipulation of the effects of glucocorticoids and other steroids in the brain and peripheral tissues.

Biography: My laboratory's major research emphasis is on glucocorticoid biology, particularly on pre-receptor metabolism by 11ß-hydroxysteroid dehydrogenases and the regulation of corticosteroid receptor expression. My colleagues and I use a range of technologies, from molecular and cell biology, through animal models (including transgenesis) to detailed clinical investigation in health and disease, to examine glucocorticoid action. Pathophysiological processes currently under investigation include: (i) the roles of glucocorticoids in early life (fetal) programming of adult disease, (ii) the role of steroids and their tissue-specific interconversion in the Metabolic Syndrome and (iii) glucocorticoids, enzymes and age-associated cognitive disorders. Funding is from a number of generous awards, including UK, European and international sources, notably Programme grants from the Wellcome Trust and MRC. We hold several patents, but have yet to get even a little rich from any of these. I am delighted to see patients with endocrine disorders several times a week to remind me of at least one reason why biomedical science and its translation matter.

Towards a pharmacotherapy of addiction

Professor Anton Schoffelmeer, Vrije Universiteit Amsterdam

Drug addiction is the most widely occurring psychiatric disorder, which continues to extract enormous human and financial costs on our western society. Thus, drug addiction places a significant burden on health, social cohesion, crime and comorbidity with other psychiatric disorders. In this respect, the most frequently abused substances are nicotine (tobacco), alcohol, cannabis, cocaine, amphetamine and heroin. Whereas numerous compounds have been screened clinically in the past, available treatments are as yet inadequate for most people and even after extended periods of abstinence, the risk of relapse to active drug use remains very high (about 90%).

The central feature of addiction is compulsive drug use, i.e. loss of control over apparently voluntary acts of drug seeking and drug taking. From a neurobiological perspective, drug addiction is a brain disease caused by persistent alterations in neuronal communication within the motivational (mesocorticolimbic) system following repeated self-administration of drugs of abuse. The case for modelling addictive processes in animals has been strongly made. Apart from their greater neurobiological accessibility, a key point is that animals can be studied from the drug naïve state through psychic dependence, whereas clinical studies begin with an addicted individual who is usually seeking help to maintain abstinence. These animal models are used to examine the role of persistent drug-induced neuroplasticity, neuronal architecture and cognitive dysfunctioning in the development and maintenance of drug-seeking behaviour in vulnerable individuals. Studying drug-, cue- and stress-induced reinstatement of drug-seeking behaviour in rats with an experience of drug self-administration, the pharmacology of relapse behaviour can now be adequately addressed. Such molecular, cellular and behavioural pharmacological studies are crucial for the development of innovative pharmacotherapeutical intervention strategies in human addicts.

Biography: Anton Schoffelmeer (1953) has had a number of post-doctoral positions over the last 20 years. From 1983 to 1988 he was a Post-doc at the Department of Pharmacology, Vrije Universiteit Amsterdam, before moving to the USA from 1989 to 1999 to undertake Post-doc training in the Department of Psychiatry at New York University, Medical Center (Professor E. J. Simon). During this time (1988–1993), he also returned to the Netherlands to become a Senior Researcher of the Royal Netherlands Academy of Arts and Sciences (KNAW). Currently, he holds different posts at the Vrije University Amsterdam: Associate Professor in Pharmacology at the Department of Medical Pharmacology (from 1993), Leader of the research program “The Pathogenesis of Drug and Alcohol Addiction” of the Neurosciences Research Institute, Vrije Universiteit (since 1997), Leader of the Psychopharmacology Section of the Department of Medical Pharmacology (since 2000) and in 2003 was made Professor of Psychopharmacology.

Discussants

Biography: **Dr Megan Holmes**, University of Edinburgh. Stress and the regulation of the hypothalamo-pituitary adrenal (HPA) axis has been a common theme throughout my research career. My PhD thesis was on neurotransmitter regulation of CRF release, under the supervision of Mortyn Jones in the University of London. Postdoctoral studies involved study of the regulation of CRF and AVP receptors in the pituitary and brain, and the factors differentially regulating CRF and AVP release from the Median Eminence. These studies were carried out at the Hungarian Academy of Sciences, Budapest and the National Institutes of Health, Bethesda, USA. Upon my return to Britain, I joined the University of Edinburgh, first on a fellowship and then as a faculty member, presently as Senior Lecturer in the Department of Clinical Neurosciences. My field of interest continues to be stress and HPA axis regulation, with particular focus on intracellular glucocorticoid metabolism and regulation of target genes in the brain including serotonin receptors.

Biography: **Dr Onno Meijer** (1967) is Assistant Professor at the division of Medical Pharmacology of the Leiden/Amsterdam Center for Drug Research, at Leiden University, the Netherlands. His research interest is the influence of glucocorticoid hormones on brain function and stress responses, with emphasis on transcriptional events that follow activation of corticosteroid receptors.

As an undergraduate he studied Medical Biology at Utrecht University (1985–1991). He obtained his PhD degree in 1996 with Dr Ron de Kloet at Leiden University, on a thesis entitled *Corticosterone and Hippocampal 5-HT1A Receptors: functional implications of central corticosteroid receptor diversity*. As a postdoc at the University of California at San Francisco he studied transcriptional regulation of the 5-HT1a receptor promoter with Drs David Pearce and Mary Dallman (1997 – 98). Since then he has been engaged in glucocorticoid sensitivity and cellular specificity in the brain, for example by studying the role of coregulatory proteins in glucocorticoid hormone action.

Biography: **Dr Melly Oitzl**, Leiden University, studied psychology with specialisation in neurophysiology and neurobiology. In 1989 she received her PhD in Psychology from the Faculty of Natural Sciences at the University of Düsseldorf (Germany). After working as a post-doctorate in the Rudolf Magnus Institute, she joined the Division in 1990, while being financed by NWO (2 projects) and EU Biotech. She was appointed as Associate Professor (Aspasia) in 2002. Her research interest focuses on the hormonal control of brain and behaviour. She studies the influence of life events (postnatal maternal deprivation, chronic stress) on neuroendocrine and behavioural adaptation, learning and memory processes in rats and (mutant) mice, particularly with respect to the function of brain corticosteroid receptors. Dr Oitzl co-ordinates the Division's research on stress, emotion and cognitive neuroscience and she regularly organizes symposia related to stress and cognition at international conferences. She is on the Editorial Board of *Behavioural Brain Research, Physiology & Behavior* and member of the Committee of the European Brain and Behaviour Society.

General Discussants

Biography: **Professor Rona Mackie CBE**, **FRSE**, International Convener, The Royal Society of Edinburgh. Professor of Dermatology and Head of Department at the University of Glasgow from 1978 to 2000. Currently, she is a Senior Research Fellow at Glasgow University in the Department of Public Health and Medical Genetics. Professor MacKie's major research interest is in the field of skin cancer, particularly malignant melanoma. She currently holds grants for both epidemiological and molecular biological research in this area. She is an active member of the European Organisation for the Research and Treatment of Cancer, and of the World Health Organisation's Melanoma Programme.

Biography: **Dr Mac Armstrong**, Chief Medical Officer for Scotland. Born in Motherwell, Lanarkshire and educated at Hamilton Academy and the University of Glasgow, Dr Armstrong qualified with First Class Honours in Physiology in 1968 and with Honours in Medicine in 1970. He was a Lecturer in Pathology in the University of Glasgow until commencing training in General Practice in 1974. He was a Principal in a large, rural, dispensing practice in North Argyll for 19 years, combining undergraduate and postgraduate teaching with growing commitments in medical politics. In 1993 he joined the staff of the BMA in London as Secretary with responsibility for the Association's 450 staff in 18 national and regional offices. He was involved in international work with the WHO, WMA and World Bank and with a number of National Medical Associations in Europe and beyond.

He became Chief Medical Officer for Scotland in January 2001, where he is the principal medical adviser to the Scottish Executive. Within the Health Department he has a particular interest in healthcare quality and standards and with the regulation, education, training and development of the medical and scientific healthcare professions.

PARTNER ORGANISATIONS:

The Royal Society of Edinburgh is Scotland's National Academy of Science & Letters. It seeks to contribute to Scotland's social, economic and cultural wellbeing. **www.royalsoced.org.uk**

The British Council is the UK's international organisation for educational opportunities and cultural relations. **www.britishcouncil.org**

The British Embassy's Science & Technology Unit has been instrumental in setting up and boosting a series of future-directed, fascinating projects exploring the galaxy of the human brain. **www.britain.nl**

The Royal Netherlands Academy of Arts and Sciences promotes Dutch science by advising government, assessing research quality, providing a forum for government, for the scientific world, promoting international cooperation and acting as an umbrella organisation for 17 scientific research institutes. **www.knaw.nl**

The Scottish Executive is the devolved government for Scotland. It is responsible for most of the issues of day-to-day concern to the people of Scotland, including health, education, justice, rural affairs, and transport. **www.scotland.gov.uk**

Scotland in the Netherlands is a ‘season’ of promotional activity, which is taking place in various towns and cities across the Netherlands from September to November 2004, and is aimed at promoting Scotland as an excellent place to live, work, study, visit and with which to do business.

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