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The Amygdala

Sainsbury Wellcome Centre

Monday 19th November 2012
Henry Wellcome Auditorium
Wellcome Collections Conference Centre
183 Euston Road, London NW1 2BE

Programme

09:00 Registration and Coffee

Session 1: Chair – John O’Keefe

09:20 **David Amaral**

“A brief overview of the organization of the amygdala in the rat, monkey and human brains”

09:45 **Joseph LeDoux**

“Emotion and Survival: What's the Connection?”

10:30 Break (Coffee/Tea)

11:00 **Andreas Lüthi**

“Defining the neuronal circuitry of fear”

11:45 **James McGaugh**

“Making Lasting Memories: Emotional Arousal and Amygdala Activation”

12:30 Lunch

Session 2: Chair – Peter Dayan

13:30 **Florian Mormann**

“A category-specific response to animals in the right human amygdala”

14:15 **David Amaral**

“The amygdala, autism and anxiety”

15:00 Break (Tea/Coffee)

15:30 **Barry Everitt**

“The amygdala and the reconsolidation of aversive and appetitive memories”

16:15 **John O’Keefe**

“Amygdala: an active memory system for ethologically-significant stimuli”

17:00 Post Meeting Discussion over Drinks and Canapes

Note: Registration and Hospitality will be in the Williams Lounge

Speakers

Professor David Amaral



David Amaral is UC Davis Distinguished Professor of Psychiatry and Neuroscience and Research Director of the MIND Institute, University of California, Davis having commenced his career with a PhD at the University of Rochester School of Medicine in 1977

His research involves multidisciplinary studies directed at determining the neuroanatomical, behavioral and electrophysiological organization and functions of brain systems that are involved in learning, memory, emotion and social behavior carried out on the human brain and on animal models. He also carries out research on the neurobiological and neuroimmune correlates of autism.

Professor Joseph LeDoux



Joseph LeDoux is a University Professor, the Henry and Lucy Moses Professor of Science, Professor of Neural Science and Psychology, and Director of the Emotional Brain Institute at New York University.

His research is aimed at understanding the biological mechanisms of emotion and its relation to memory. He is particularly interested in how the brain learns and stores information about threats. Using classical fear conditioning as way of inducing memories about past threats in rats, he has mapped the neural pathways by which sensory stimuli enter and flow through the brain in the process of fear learning. This work implicated specific circuits and cellular and molecular mechanisms within the amygdala as essential for the formation of memories about the fear conditioning experience. The same

brain system, to a first approximation, appears to underlie fear learning in humans. The detailed mechanisms of fear, which can only be uncovered through animal studies, are thus applicable to fear processing in the human brain and provide a foundation for understanding fear and other emotional disorders.

Professor Andreas Lüthi



Andreas Lüthi completed his PhD in 1996 at the University of Basel. Since 2005 he has been a Senior Group Leader, Friedrich Miescher Institute for Biomedical Research, Basel

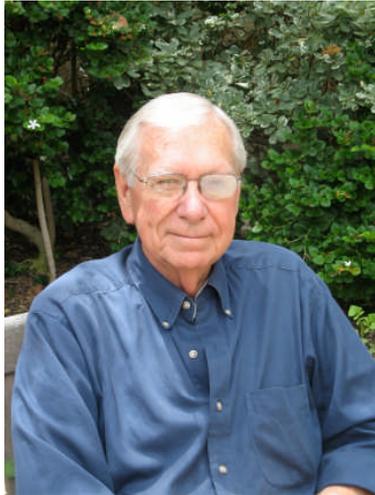
His research interests are in the cellular mechanisms of learning and memory. Experience-dependent changes in behavior are mediated by long-term functional modifications in brain circuits.

They are interested in understanding the underlying mechanisms at the molecular, cellular and circuit levels. As a model system, they are using classical (Pavlovian) fear conditioning, a simple form of associative learning that is particularly suitable for study in rodents.

The inability to control or inhibit inappropriate fear responses is a hallmark of human anxiety disorders. They are investigating the cellular mechanisms underlying fear extinction, an associative learning process mediating inhibitory control of inappropriate fear behavior.

Using a multidisciplinary and integrated experimental approach in mice, they are combining in vitro and in vivo electrophysiology, imaging, molecular biology, genetics, and behavioral techniques to identify the synaptic and cellular constituents of neural circuits in the amygdala underlying the acquisition, encoding and extinction of fear memory - the microcircuitry of fear conditioning.

Professor James McGaugh



James McGaugh is Research Professor, Neurobiology and Behavior in the School of Biological Sciences and Fellow of the Center for the Neurobiology of Learning and Memory, University of California, having commenced his career with a Ph.D. in Physiological Psychology at the University of California in Berkeley in 1959. He is a member of the U.S National Academy of Science (1989)

Research in his laboratory has focused on the interaction of the amygdala with other brain regions in regulating memory storage. Findings of recent experiments indicate that the amygdala influences memory by modulating the functioning of other brain regions involved in information storage.

Dr Florian Mormann



Florian Mormann completed undergraduate and post graduate studies in Physics and followed his PhD with an M.D. in medicine. Following a number of postdoctoral roles, fellowships and clinical appointments including work with Christof Koch and Itzhak Fried, he took up a position in the Dept. of Epileptology at the University of Bonn in 2009. In 2012 he was awarded an associate professor position by the Lichtenberg programme of the Volkswagen Foundation.

His current research focuses on recordings of single-unit activity and local field potentials in the human medial temporal lobe to better understand perception, memory, and mechanisms of seizure generation.

Professor Barry Everitt

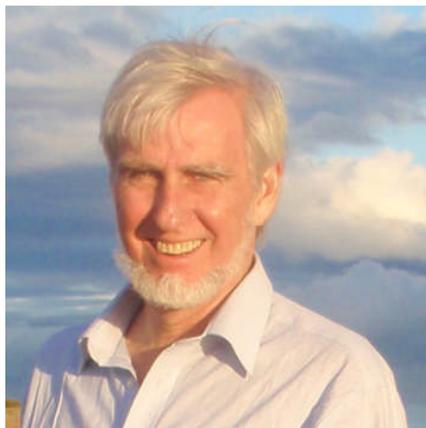


Barry Everitt FRS., FMedSci. is Professor of Behavioural Neuroscience at the University of Cambridge.

Following his Ph.D. at Birmingham he undertook post-doctoral research at Birmingham and then at the Karolinska Institute in Stockholm. He was appointed to the Department of Anatomy at the University of Cambridge in 1974, moving to the Department of Experimental Psychology in 1998.

His research is in the general area of behavioural neuroscience and is concerned with the neural and psychological mechanisms underlying learning, memory and motivation, especially in the context of drug addiction.

Professor John O'Keefe



John O'Keefe, FRS, FMedSci is Professor of Cognitive Neuroscience at UCL

Following his Ph.D at McGill, he joined UCL in 1967 as a USNIMH postdoctoral fellow and has been there ever since, becoming a Professor in 1987. He is currently Interim Director of the Sainsbury Wellcome Centre for Neural Circuits and Behaviour.

O'Keefe discovered that hippocampal pyramidal cells respond selectively to an animal's spatial location and suggested that this part of the brain might function as a cognitive map, a notion developed extensively by O'Keefe and Nadel ([www.cognitive map.net](http://www.cognitive-map.net)). He has

recently turned his attention to the amygdala, using a neuroethological approach similar to that originally developed for his hippocampal studies.

The amygdala, a prominent part of the limbic system, has been implicated in a diverse set of biologically important functions ranging from aversive emotions, through consolidation of memories, to the identification of ethologically relevant stimuli. The meeting collects together some of the leading theoreticians and experimenters exploring these and other functions of the amygdala. A lively exchange of ideas and data is predicted.

Abstracts

Professor Joseph LeDoux
New York University

“Emotion and Survival: What's the Connection?”

Darwin proposed that emotional states of mind (feelings like fear or pleasure) help organisms adapt and survive. This equation of emotions with survival has guided the field ever since. It is now common to use so-called emotional responses as a way of identifying brain circuits that give rise to innate emotional states of mind, such as feelings of fear in the presence of threats. But there is actually little evidence that feelings like fear are hard-wired in the brain and inherited from our mammalian ancestors. What we have inherited, instead, are circuits that detect and respond to threats in preprogrammed yet modifiable ways. Threat detection sets off a cascade of responses in the body and within the brain that serve as physiological ingredients that compel us to feel afraid when these non-emotional ingredients are blended in conscious experience. Included amongst such ingredients are: information about the stimulus and the physical and social context, survival circuit activity, changes in brain arousal, feedback from bodily responses, memory retrieval, and cognitive processes that evaluate and assess the significance of these various ingredients. Different emotions, and even different variants of a given emotion like fear (trepidation, panic, terror), have different blends of these non-emotional ingredients, resulting in different feelings. The mechanisms that give rise to emotional feelings are thus not the same as the mechanisms that give rise to innate survival responses. Examples of survival circuits, other than threat/defense circuits), are those involved in managing energy, fluid balance, thermoregulation, and reproduction. Survival circuits are conserved in mammals and to a large extent across vertebrates. Although invertebrates have different nervous systems and thus different circuits than vertebrates, they nevertheless have their own circuits for managing the same fundamental tasks (survival functions) necessary for life. Indeed, even unicellular organisms have to solve similar life tasks. We should be asking which circuits and functions present in other animals are also present in humans, not whether fear or other human emotions are present in other mammals. Whether other animals have feelings is not a question about whether they have survival circuits but instead about whether they have consciousness, and if so, the nature of the kind of experiences that result, which is something we may never know.

Professor Andreas Lüthi
Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

“Inhibition in neuronal networks of fear”

Classical fear conditioning is one of the most powerful models for studying the neuronal substrates of associative learning and for investigating how plasticity in defined neuronal circuits causes behavioral changes. In animals and humans, the amygdala is a key brain structure within a larger neuronal network mediating the acquisition, expression and extinction of fear memories. This presentation will review emerging concepts in the organization and function of the neuronal circuitry of fear learning and extinction. In particular, I will summarize recent progress in understanding how switches in the activity of distinct types of amygdala neurons mediate rapid changes in fear behavior. I will show that functionally, anatomically and genetically defined types of amygdala neurons are precisely connected within the local circuitry and within larger-scale neuronal networks and that they contribute to specific aspects of fear learning and extinction. Finally, I will discuss how local inhibitory circuits contribute to the acquisition and expression of fear and extinction memories by multiple mechanisms and

at multiple levels both in the amygdala and in other brain areas. The presentation aims at illustrating how the convergence of molecular, electrophysiological and optical approaches has enriched our understanding of the neuronal basis of fear conditioning and of learning and memory in general.

Professor James McGaugh
Center for the Neurobiology of Learning and Memory
University of California, Irvine

“Making Lasting Memories: Emotional Arousal and Amygdala Activation”

Emotionally arousing experiences create lasting memories. Extensive evidence indicates that the basolateral complex of the amygdala (BLA) plays a critical role in modulating the consolidation of memories of emotionally arousing experiences. The evidence also indicates that adrenal stress hormones released by emotional arousal regulate memory consolidation via converging influences on β -noradrenergic activation within the BLA. Activation of the BLA enhances memory for many different types of training experiences via projections to other brain regions involved in processing different aspects of memory. Thus, the findings of both animal and human studies provide compelling evidence that stress-induced activation of the BLA and its projections to other brain regions plays a critical role in insuring that emotionally significant experiences are well-remembered.

Dr Florian Mormann
University of Bonn

“A category-specific response to animals in the right human amygdala”

The human amygdala has been implicated in the processing of biologically relevant information, including both aversive and appetitive stimuli. Earlier notions that the amygdala might be specialized to mediate fear responses are at odds with more abstract accounts whereby the amygdala processes ambiguity or unpredictability in the environment and mediates an organism's vigilance and arousal.

To test whether neurons in the human amygdala show preferential responses to particular stimulus categories, we recorded from the MTL in 41 neurosurgical patients undergoing epilepsy monitoring. Subjects viewed stimulus sets containing images of persons, animals, landmarks, or objects. We recorded from over 3500 neurons in the amygdala, hippocampus and entorhinal cortex. Of these, 460 units (more than 100 per region) responded significantly to one or more of the presented stimuli.

Neurons in the amygdala responded preferentially to pictures of animals rather than to pictures of other stimulus categories. These preferential neuronal responses to animals were exclusive to the right amygdala, neurons in the left amygdala showed no category preference. Amygdala neurons responded faster to animal pictures than to stimuli from other categories, although response latencies in general were concordant with cortical rather than fast subcortical processing. To rule out an influence of emotional dimensions within our stimuli, we reproduced an animal versus non-animal category effect in the right amygdala in an additional functional magnetic resonance imaging (fMRI) control experiment using stimuli that were controlled for emotional valence and arousal.

Our results demonstrate a previously unknown role of the right amygdala in processing animals that could reflect the broad ancestral significance of this stimulus category in our exploration of the environment. Although the category response to animals was independent of emotional content, we believe that the phylogenetic significance of animals, which could represent either predators or prey, resulted in neural adaptations for the dedicated processing of these biologically salient stimuli and the amygdala could plausibly be a part of the network implementing these mechanisms.

David G. Amaral, Ph.D.
The M.I.N.D. Institute, UC Davis

“The amygdala, autism and anxiety”

This presentation will first provide a brief overview of the features of autism spectrum disorder. I will then explore literature and original magnetic resonance imaging and postmortem histological research indicating that the amygdala is indeed pathological in autism. There is abnormal development of the amygdala in young individuals diagnosed with autism and an apparent decrease of neurons in the mature amygdala in autism. I will then review studies carried out in nonhuman primates to evaluate what functional disturbances could result from amygdala pathology. Data indicate that the amygdala may contribute to comorbid anxiety in autism rather than one of the core features of the disorder.

Professor Barry Everitt
Department of Experimental Psychology
University of Cambridge

“The amygdala and the reconsolidation of aversive and appetitive memories”

Consolidated memories can, under some circumstances, become labile – or destabilised - at retrieval and must undergo a restabilisation process to persist in the brain. This restabilization process has become known as reconsolidation, a disruption of which leads to amnesia. I will discuss experiments using psychologically well-characterised behavioural procedures, which have demonstrated a requirement for a specific protein, ZIF268, (the protein product of the immediate-early gene *zif268*) in the amygdala in the reconsolidation of cued fear and drug memories. For example, infusion of Zif268 antisense oligodeoxynucleotides into the basolateral amygdala, prior to the conditioned stimulus (CS) presentation-evoked reactivation of a fear memory results in the loss of fear following subsequent presentation of the fear CS. Knockdown of the same gene on reactivation of a CS-cocaine memory results in the loss subsequently of the acquired conditioned reinforcing properties of the drug-associated stimulus and a reduction in drug seeking behaviour. Antagonism of glutamate transmission at NMDA receptors or adrenergic transmission at β -adrenoceptors also prevents the reconsolidation of CS-fear and CS-drug memories and, in the case of NMDA receptor blockade, this is associated with reduced expression of *zif268* in the amygdala, suggesting a link between neurotransmission events and intracellular signaling that are engaged at memory retrieval and result in restabilisation of the memory. These experimental data suggest the possible utility of targeting reconsolidation in the treatment of neuropsychiatric disorders that are characterized by maladaptive and intrusive memories. These include post-traumatic stress disorder as well as drug addiction in which drug-associated stimuli evoke memories of prior drug use, craving and relapse to drug use.

Professor John O’Keefe
Sainsbury Wellcome Centre, UCL

“Amygdala: an active memory system for ethologically-significant stimuli”

The amygdala has been assigned a variety of functions including a role in fear conditioning, feeding, sexual behavior, and social interactions. I will report findings from single unit recordings in the amygdala of the behaving male rat during a battery of tests including: interactions with a female rat, ingestion of sweetened rice and other foods, a brief mild tail pinch, challenge with a mildly aversive air can nozzle, auditory stimuli including pure tone ramps, and placement in a different enclosure (usual transport box). Aside from the transport box, all other stimuli/events occurred while the animal was sitting on a small elevated platform. I report the existence of amygdala cells responsive to one or more of these events. While some were responsive during several events, the majority were more selective, responding only to one event eg to eating food or to interactions with the rat. Further, some cells

discriminated within each category, eg a cell which discriminated between a specific female rat and other rats. Significantly, few cells responded consistently during different events with the same valence eg to both eating and interacting with the female rat, suggesting that the amygdala is not primarily involved in specific emotions or valences per se. In 2/3 of responsive neurones, the altered firing rates were maintained for considerable periods of time following the termination of the eliciting event (typically for 60 - 120 sec, maximum 1250 sec). This aftereffect activity was relatively insensitive to the animal's ongoing behaviour, supporting the argument that it represented a pure memory for the event. I propose that the amygdala acts as an active memory buffer for the maintenance of traces of ethologically-significant stimuli or events.