A meeting to remember

Meeting on Memory and Related Disorders

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Introduction

Blustery Madrid winter days, traffic-congested streets and an encounter with dysfunctional public transport are difficult to forget. Fortunately, the approximately 50 scientists that gathered in the city for the workshop on 'Memory and Related Disorders' also took away memories of outstanding presentations and vigorous discussions. The workshop tackled a diverse set of topics including: the neural systems involved in declarative and emotional memories; the cellular and molecular correlates of memory and their modulation by

drugs of abuse; memory phases; and the effects on the cellular and neural systems of ageing and neurodegenerative and neurodevelopmental diseases. Diverse experimental disciplines represented at the meeting—such as bioinformatics, biophysics, cell and molecular biology, experimental psychology, genetics, neuroimaging, neuroethology, pharmacology and physiology—provided a rich tapestry depicting the encoding and maintenance of memories, and the diseases that subvert these processes.

Neural bases of declarative and emotional memories

Studies of the mammalian mechanisms of memory have focused on the hippocampus, the perirhinal and parahippocampal cortices of the temporal lobe, the amygdala, the olfactory, prefrontal and visual cortices, and the cerebellum (Fig 1). The first session of the meeting examined the neural systems that process different types of memory in humans. The studies that were discussed used neuroimaging, clever psychological paradigms and pharmacological interventions to try to traverse the gulf between descriptive studies and insights into the mechanisms involved. Using functional magnetic resonance imaging (fMRI) and anatomically constrained magnetoencephalography (which captures signal changes with a fast onset), A. Wagner (Stanford, CA, USA) examined the mechanisms of the human medial temporal lobe (MTL), which builds and retrieves memories. Activation patterns during the encoding of words differ for subsequently remembered and forgotten experiences, and the magnitude of activation in the left inferior prefrontal and left parahippocampal cortices during an experience is correlated with the subsequent ability to remember that experience. Activations in distinct MTL structures during memory formation reflect the ability to recognize a previously encountered item and to recollect its specific contextual details (Davachi *et al*, 2003). Encoding activation (increases in fMRI signal) in the hippocampus and posterior parahippocampal cortex predicted only contextual recollection whereas activation in the perirhinal cortex predicted only item recognition. Representation of memory strength is signalled rapidly in the MTL through 'repetition suppression'-mediated decreases in activation, conveying the subjective perception of stimulus familiarity or novelty (Gonsalves *et al*, 2005).

E. Phelps (New York, NY, USA) presented her research, which also uses state-of-the-art fMRI techniques, on how the hippocampus and amygdala interact to modulate emotional memories and the

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Fig 1 | Traditional classification of long-term memories and the brain structures that are thought to be central to these processes. In addition to its role in implicit emotional learning and memory, the amygdala has a role in the emotional modulation of explicit memory, attention and perception, social behaviour, and the inhibition and regulation of responses. The reciprocal projections between nuclei of the amygdala and regions of the hippocampal cortices, which represent a subset of the information flow to and from the amygdala that contributes to these diverse processes are shown in blue.

subjective feeling of remembering (Phelps, 2004). The amygdala can modulate both the encoding and the storage of hippocampal-dependent memories. By forming episodic representations of the emotional significance and interpretation of events, the hippocampus can influence the amygdala's responses to emotional stimuli. Emotional photographs enhance the subjective feeling of remembering but not the accuracy. Neutral photographs elicit enhanced fMRI activation in the parahippocampal cortex, whereas emotional photographs are associated with enhanced activity in the amygdala, suggesting that subjects rely on arousal and perceptual fluency to evaluate these memories (Sharot *et al.*, 2004). R. Dolan (London, UK) analysed emotion-induced enhancements or decrements in memory. Enhanced memories of emotional words depend on β -adrenergic signalling and are at the expense of memories that precede the emotional stimulus. Compared with neutral stimuli, these emotional stimuli increased amygdala fMRI activation during encoding, and hippocampal activation during retrieval. These amygdala–hippocampal interactions depend on β -adrenergic stimulation at encoding but not retrieval (Strange & Dolan, 2004). With a recall paradigm that measured magnitude of retrograde (preceding) and anterograde (following) interference of emotion on memory, negatively valenced (emotional value)

stimuli produced retrograde amnesia, whereas positively valenced items produced retrograde hyperamnesia; arousal produced anterograde amnesia, targeting anterograde encoding of memories. Double-blind randomized administration of propranolol (a β -blocker), reboxetine (a noradrenergic re-uptake inhibitor) or placebo suggested that the effects of emotions on memory depend on the central nervous system noradrenergic modulation of arousal (Hurlemann *et al.*, 2005).

Animal models provided complementary insights to these studies but with some problems. Damage to the hippocampus typically produces temporally graded retrograde amnesia, whereby recently acquired memories are impaired more than memories acquired remotely. However, temporally graded retrograde amnesia after hippocampal damage has not been shown in rodents in spatial tasks such as the water maze (Clark *et al.*, 2005a). R. Clark (San Diego, CA, USA) tackled the issue of why spatial memory becomes hippocampal-independent in humans but not in rodents. Typically, spatial learning in rodents occurs during a limited period of time when the animals are adults, whereas the human studies involve information acquired over many years. Even after extended training, beginning early in life, and with a prolonged training-surgery interval, hippocampal lesions still impair the performance of rodents in the

water-maze task (Clark *et al*, 2005b). The water-maze tests of remote spatial memory might entail new learning abilities because the rodent must continually update its location in space to perform well in the retention test. Patients with hippocampal lesions, however, do not need to acquire new information to answer questions about their remote spatial memory. M. Fanselow (Los Angeles, CA, USA), also using rodent models, examined the contributions of the hippocampus and basolateral amygdala (BLA) in context (with a shock delivered in a specific location) and trace (for example, with a brief interval between light and foot-shock) fear conditioning. In response to shock treatment, rats with BLA lesions failed to freeze when tested at recent and remote intervals, supporting a role for the BLA in the permanent storage of fear memory (Gale *et al*, 2004). Pavlovian conditioning has a component of episodic memory that is hippocampal-dependent. The dorsal hippocampus is crucially involved in the acquisition and expression of trace and contextual fear conditioning, and N-methyl-D-aspartate (NMDA) glutamate receptor-mediated transmission seems to contribute to synaptic plasticity and long-term memories (Quinn *et al*, 2005). When infused into the dorsal hippocampus before conditioning and/or testing, the NMDA receptor antagonist, D,L-2-amino-5-phosphonovaleric acid (APV), disrupted acquisition but not expression of contextual fear conditioning. By contrast, APV attenuated both acquisition and expression of trace fear memories. CA1-specific deletion of the NMDA receptor 1 (NMDAR1) subunit also affected contextual conditioning in these mice.

Synapses, genes, molecules and signalling cascades

The second main focus of the meeting was the discussion of the molecular and cellular aspects of memory formation and storage (Fig 2). J. Lerma (San Juan de Alicante, Spain) and Y. Ben-Ari (Marseille, France) explored different aspects of neuronal function and excitability with important consequences for synaptic plasticity. Through the use of a pertussis-toxin-sensitive G-protein-dependent modulation of Ca^{2+} channels, Lerma discussed the contribution of non-canonical signalling by kainite subtype glutamate receptors to synaptic plasticity and to the release of several transmitters (Rozas *et al*, 2003). Ben-Ari presented innovative work on brain development and epilepsy using organotypic cultures. Adult neurons are inhibited by γ -aminobutyric acid (GABA), whereas it excites immature neurons. On the basis of these results, Ben-Ari suggested that GABA and NMDA receptors together shape immature hippocampal circuits and sometimes lead to the formation of epileptic foci.

Several presentations illustrated the power of bottom-up approaches: using genetically engineered mice to analyse learning and memory. K.P. Giese (London, UK) combined a sophisticated genetic manipulation with a thoughtful behavioural analysis to provide insights into memory formation. A 'knock-in' mutant mouse—whose calcium-calmodulin-dependent kinase II α (*CaMKII α*) gene lacked the enzyme autophosphorylation site—debunked the proposal that autophosphorylation of *CaMKII α* has a role in memory storage. Analysis of these mutant mice in hippocampus- and amygdala-dependent learning and memory tasks showed that the autophosphorylation of *CaMKII α* is required for rapid learning but not essential for memory formation (Irvine *et al*, 2005). Repeated training activates parallel molecular cascades in memory formation and overcomes the *CaMKII α* autophosphorylation deficit. Long-term storage of memories also requires *de novo* gene expression. A. Barco (San Juan de Alicante, Spain) characterized CREB-binding protein (CBP)-deficient mice, which are a mouse model for the Rubinstein-Taybi mental retardation syndrome

(RTS). CBP-deficient mice had long-term potentiation (LTP) and memory deficits, which correlated with deficits in chromatin acetylation that could be reversed by a histone deacetylase inhibitor (Alarcon *et al*, 2004). On the basis of evidence from the RTS mouse model and data from other groups, Barco proposed that chromatin remodelling is central to synaptic plasticity and memory, and that other epigenetic mechanisms might also regulate memory. As transcription is required for long-lasting plasticity and memory formation, signals generated at the synapse must effect changes in the nucleus. K. Thompson (Los Angeles, CA, USA) discussed the role of importins—a family of soluble nuclear transport factors—in the translocation of signalling proteins to the nucleus. Using photo-activatable green fluorescent protein (GFP) in hippocampal neurons, she showed that NMDAR activation, but not depolarization, induced importin-dependent nuclear translocation. LTP-inducing stimuli in hippocampal slices and long-term facilitation in *Aplysia* sensory-motor synapses also require active nuclear import (Thompson *et al*, 2004).

L. de Lecea (La Jolla, CA, USA) showed that transgenic mice that overexpress cortistatin (a neuropeptide similar to somatostatin) exhibit diminished locomotor activity, enhanced slow-wave sleep, LTP deficits in the dentate gyrus and impairment of hippocampal-dependent spatial learning (Tallent *et al*, 2005). Pharmacological application of cortistatin to hippocampal slices mimicked these LTP deficits. de Lecea proposed that the increase in hippocampal cortistatin expression observed during ageing might contribute to age-related cognitive deficits. Several talks discussed other aspects of memory dysfunction during ageing. M. Gallagher (Baltimore, MD, USA) showed that elderly rats exhibited memory impairment similar to that caused by mild temporal lobe dysfunction (Gallagher 1997; Gallagher *et al*, 2003). Mechanisms for long-term depression differ in aged rodents that maintain cognitive performance compared with those in young adult rats. Her data suggest that cognitive abilities might be sustained in aged individuals by a switch in synaptic plasticity mechanisms (Lee HK *et al*, 2005). A. Ferrus (Madrid, Spain) characterized *Drosophila* mutants with an increased number of synapses and alluded to how age-related deficits might be reversed. The *Drosophila* mutant *gigas* exhibited an enlargement of postmitotic cells caused by additional rounds of DNA replication (Canal *et al*, 1998). Mosaic adult flies with one of two antennae homozygous for the *gigas* mutation had a normal number and type of sensory afferents and projections to the olfactory glomeruli, but had more branches in the glomeruli than those of wild-type flies. Odorant tests of *gigas* mutants showed attractive and repulsive responses to concentrations of the odorants that did not affect the controls. Ferrus concluded that these results suggest a mechanism by which flies increase the number of functional synapses in adult animals and so compensate for the loss that is associated with age-related cognitive decline. I. Slutsky (Cambridge, MA, USA) suggested a new role for magnesium in the maintenance of memory function in middle age and beyond. Low concentrations of Mg^{2+} lead to a reduction in the number of synapses, whereas high Mg^{2+} leads to an increase in the number of synapses. These effects are mediated by upregulation of the NMDAR subunit NR2B (Slutsky *et al*, 2004). Maintaining adequate levels of Mg^{2+} in the cerebrospinal fluid might be essential for maintaining the plasticity of synapses, but whether such a deficit in Mg^{2+} affects memory function in elderly people has not yet been shown.

Synaptic plasticity is also involved in other important neuronal processes related to memory formation. T. Hisatsune (Tokyo, Japan) examined how patterned electrical activity influences hippocampal

Fig 2 | Crucial steps mediating changes in synaptic plasticity correlated with memory formation. Outlined are some of the cellular and molecular mechanisms contributing to memory storage that have been identified in hippocampal CA1 pyramidal neurons and other model systems, and were discussed at the meeting. AC, adenylyl cyclase; AMPA-R, α -amino-5-hydroxy-3-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; CaMKII α , calcium-calmodulin-dependent kinase II α ; CBP, CREB-binding protein; CREB, c-AMP response element binding protein; GABA-R, γ -aminobutyric acid receptor; mGlu-R, metabotropic glutamate receptor; NF- κ B, nuclear factor- κ B; NMDAR, N-methyl-D-aspartate receptor; PKA, protein kinase A; SRF, serum response factor; tPA, tissue plasminogen activator.

neurogenesis in the subgranular zone of the adult dentate gyrus. This neurogenesis progresses from radial glia-like stem/progenitor cells to transiently amplifying neuronal progenitor cells and then to postmitotic neurons. Electrical recordings in hippocampal slices from nestin-GFP mice showed that these neuronal progenitor cells receive excitatory GABAergic inputs; GABA is excitatory in immature neurons because of elevated intracellular Cl⁻ activation of

these excitatory inputs leads to Ca²⁺-mediated increase in neurogenic basic helix-loop-helix protein (NeuroD) and differentiation to granule cells in the dentate gyrus (Tozuka *et al*, 2005). Electrical pulses of 4–7 Hz (θ burst) facilitation of GABA release onto progenitors initiates this process. Hippocampal θ rhythms—for example, exploratory behaviour and rapid eye movement sleep—might promote hippocampal neurogenesis.

Changes in synaptic plasticity and associative learning and memory share molecular mechanisms with the cascade of events triggered by drugs of abuse (Jones & Bonci, 2005). A. Bonci (San Francisco, CA, USA) highlighted the role of orexin A in the potentiation of NMDAR-mediated neurotransmission and the efficacy of orexin receptor antagonists in the blockade of cocaine-induced behavioural sensitization. This *in vitro* and *in vivo* evidence for the role of orexin in ventral tegmental area neural plasticity has direct relevance to drug addiction (Borgland *et al*, 2006).

Analysing memory phases

Several laboratories have evidence that established memories, once recalled, become labile and sensitive to disruption, and require reconsolidation to become permanent. Y. Dudai (Rehovot, Israel) examined reconsolidation of conditioned taste aversion in rats (Berman *et al*, 2003; Dudai, 2004; Dudai & Eisenberg, 2004) and showed that reconsolidation occurs only in recently recalled memories and that its inhibition does not cause permanent amnesia. During the discussion, Dudai challenged one of the perceived dogmas in the field—the requirement of *de novo* gene expression for the formation of memory traces—and concluded that reconsolidation is a manifestation of lingering consolidation, rather than the recapitulation of the same sequence of molecular and cellular events. J.L. Lee (Cambridge, UK) discussed the molecular basis of consolidation and reconsolidation of aversive and positive taste associations. By infusing antisense oligodeoxynucleotides into the hippocampus of rats, Lee showed that consolidation and reconsolidation could be dissociated at the molecular level into two independent components of memory storage. Consolidation involves brain-derived neurotrophic factor (BDNF) but not the transcription factor Zif268, whereas reconsolidation recruits Zif268 but not BDNF (Lee *et al*, 2004). Therefore, memories could be disrupted after their acquisition and consolidation by impairing their reconsolidation. The association between drug availability and a conditioned stimulus undergoes reconsolidation in a manner similar to aversive memories. Infusion of Zif268 antisense oligodeoxynucleotides into the BLA, before the reactivation of a well-learned memory for a conditioned stimulus associated with cocaine, abolished the conditioned reinforcing properties of the drug-associated stimulus (Lee *et al*, 2005).

A. Pascual (Seville, Spain) examined the memory phases in *Drosophila* (Pascual & Preat, 2001) and showed that two types of memory—anaesthesia-resistant memory (ARM) and stabilized long-term memory (LTM)—rely on independent mechanisms. The previous model for memory formation in flies proposed that training induces learning through a sequential pathway, from short-term memory (STM), to middle-term memory (MTM) to ARM, and, through repeated and spaced training, terminates in LTM. ARM and LTM were thought to derive from MTM and to coexist after spaced conditioning. However, in flies that are devoid of mushroom body vertical lobes and so cannot form LTM, Pascual showed an interesting paradox: the more the flies are trained, the less they remember (Isabel *et al*, 2004). Pascual proposed that the formation of LTM causes the extinction of ARM; ARM acts as a gating mechanism to ensure that LTM is formed only after an animal is exposed to the same experience many times. This study also highlights how *Drosophila* is useful not only for genetic screens but also for anatomically based studies of learning and memory.

Memory-related disorders

The meeting closed with a session on neurodegenerative and neurodevelopmental diseases. M. Goedert (Cambridge, UK), compared the two most prevalent neurodegenerative disorders: Alzheimer and Parkinson diseases. Parkinson disease is defined by the presence of intra-cytoplasmic filamentous inclusions known as Lewy bodies, which are composed predominantly of α -synuclein (Goedert, 1999; Goedert *et al*, 2000; Spillantini & Goedert, 2001). Using the fronto-temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) as an elegant link between Parkinson disease and Alzheimer disease, he explained the role of tau protein in Alzheimer disease, FTDP-17 and Pick disease, indicating that different missense mutations in tau give rise to a clinical and neuropathological phenotype reminiscent of Pick disease. Overproduction of tau with four tubulin-binding repeats can lead to the pathogenesis of other tauopathies, such as supranuclear palsy or corticobasal neurodegeneration. O. Lazarov (Chicago, IL, USA) and J. Avila (Madrid, Spain) examined different mouse models for Alzheimer disease. The progressive memory loss and cognitive deterioration in Alzheimer disease are attributed to lesions in the association cortex, the entorhinal cortex and the hippocampus (Lazarov *et al*, 2005, 2006). Entorhinal cortex neurons are most vulnerable to a lesion of the perforant pathway, which forms the main input to the hippocampus. Using this paradigm, Lazarov showed that mutant presenilin 1 enhances this perforant pathway lesion and neuronal loss in the entorhinal cortex. Avila presented the generation and characterization of a transgenic mouse that could be induced to overexpress glycogen synthase kinase 3 (GSK3). GSK3 mediates the hyperphosphorylation of tau, and its overexpression leads to behavioural deficits in the Morris water maze and object recognition tasks; some of these behavioural and pathological deficits could be reversed when GSK3 levels returned to normal (Engel *et al*, 2006; Hernandez *et al*, 2002).

G. Gasic (Boston, MA, USA) examined neurodevelopmental and neurodegenerative aspects of alcohol and drug addiction in humans. High-resolution MRI of cocaine addicts and matched controls reveals that cocaine addicts have volume, topology and symmetry differences in their amygdala, which do not correlate with any measures of drug use such as age of initiation, frequency of use and amount of cocaine (Makris *et al*, 2004). Gasic considered a neurodevelopmental and a neurodegenerative interpretation of these data. The former was favoured as there was no correlation with any measure of drug use and the amygdala asymmetry that develops during adolescence was absent. As cocaine addicts often abuse alcohol, a cohort of alcohol-dependent subjects was compared with matched controls, and amygdala volume and topology (which are different from cocaine-dependent subjects) differences were observed that predicted a risk of relapse in abstinent alcoholics. Interactions between the BLA and the orbitofrontal cortex are important for signalling potentially negative outcomes, which might be impaired preceding and/or following substance abuse (Schoenbaum *et al*, 2003, 2004).

Concluding remarks

Half a century ago, William Beecher Scoville and Brenda Milner described 'H.M.', who had surgery for intractable epilepsy that decreased his frequency of seizures but left him without part of his MTL bilaterally (Scoville & Milner, 1957). The authors ascribed his severe anterograde amnesia and other memory deficits to the loss of his hippocampal formation despite the removal of other structures in the MTL. Shortly after this landmark paper on systems neurobiology of

memory, several studies revealed the crucial role of RNA and protein synthesis in memory formation (Agranoff & Klinger, 1964; Barondes & Jarvik, 1964; Flexner *et al*, 1963; Squire & Barondes, 1970). Since these seminal studies, bottom-up and top-down approaches have contributed to our understanding of the cellular and molecular mechanisms underlying memory formation. This meeting clearly revealed the power of both reductionist approaches in animal models and state-of-the-art, non-invasive imaging techniques in the working human brain. The convergence of experimental psychology and functional systems biology is leading to a new synthesis of knowledge about how the brain works. Looking forwards, we need to be able to combine studies at the level of neural systems, the genes that are involved in their development and maintenance, and the environment in which behaviour occurs. These studies will rely on the continuous improvements in brain imaging techniques and in an understanding of the intra- and extracellular signalling cascades, how they are affected by genetic variations, and how they are linked to the distributed neural systems that mediate not only information storage but also complex behaviour.

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