Response: The birth of a memory

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Otten and Rugg have elegantly integrated the results of the study by Fell and colleagues [1] into the current knowledge about how experiences are transformed into memories. One of their central conclusions is that the findings ‘point to the involvement of anterior MTL [medial temporal lobe] cortex as well as the hippocampus in the initial stages of memory formation.’ Despite these important aspects of localization and of the temporal sequence of MTL substructure involvement [2], we would like to highlight another central aspect of that study: namely, that a particular parameter of neuronal activity, rhinal–hippocampal phase-synchronization in the gamma-frequency band (~40 Hz), correlated with subsequent recall. This is conceptually important because memories might reside in neuronal assemblies rather than in individual neurons [3], and synchronization is an ideal mechanism to bind neurons into assemblies [4].

In early visual processing, neurons that encode features of a complex visual percept are associated in functional assemblies through gamma-frequency synchronization [5]. Furthermore, when sensory stimuli are perceptually or attentionally selected and the respective neurons are bound together to raise their salience, gamma-frequency synchronization among these neurons is also enhanced [5]. Gamma-mediated coupling, and its modulation by attention, is not limited to the visual modality: it is also found in the auditory [6] and somatosensory domains [7]. Moreover, gamma oscillations allow visuo-motor binding between posterior and central brain regions [8] and are involved in higher order cognitive operations, such as working memory [9] or learning of new associations in a conditioning task [10].

In addition to being a means for dynamically binding neurons into assemblies, gamma-frequency synchronization appears to be the prime candidate mechanism for stabilizing cortical connections among members of a neural assembly over time. On the one hand, neurons increase or decrease the strength of their synaptic connections depending on the precise coincidence of their activation [11] and gamma-frequency synchronization provides exactly the required temporal precision. On the other hand, strengthened connections among neurons in a ‘memory assembly’ might facilitate its later recall.

In general, EEG signals reflect postsynaptic potentials, which are mainly determined by the average activity of local neuronal populations [12]. In other words, EEG oscillations of ~40 Hz are based on clusters of discharges occurring about every 25 ms. Although the exact mechanisms underlying the generation of gamma-frequency synchronization are as yet unclear, several studies have begun to shed light on this issue. In the hippocampus, gamma-frequency synchronization is driven by interneuron network oscillations and intrinsic membrane resonance, as revealed in slice preparations [13]. Bragin and colleagues [14] have identified gamma-activity in the hippocampus of behaving rats and have shown that gamma-activity is most prominent in the dentate gyrus, the main hippocampal recipient of input from the neocortex via the entorhinal cortex and perforant path [15].

With regard to ‘phase locking of gamma-activity,’ Otten and Rugg state that its ‘functional significance, origin and relationship to subsequent memory effects seen in other measures are uncertain.’ However, taking the previously mentioned findings into account, we arrive at a different conclusion. Several lines of evidence suggest that gamma-frequency synchronization plays a general role in binding neurons into assemblies over short and long distances. In memory formation, gamma activity has the optimal frequency to support the transformation of a temporary representation into a durable memory trace by strengthening synaptic connectivity. Therefore, we hypothesize that the rhinal–hippocampal coupling observed by Fell and colleagues [1] enables information transfer to the hippocampus and initiates the mnemonic operation of memory encoding, which leads to synaptic plasticity and occurs within the first second of an event that can be remembered later on.

References
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Competing on the edge

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Fast-acting neurotransmitters can exit the synaptic cleft and bind to extrasynaptic receptors. This process is modulated by transmitter uptake mechanisms (transporters). A new study focusing on glutamate-mediated transmission in the cerebellum describes the specific role of neuronal transporters in modulating the access of glutamate to extrasynaptic metabotropic glutamate receptors, and reveals important consequences of extrasynaptic signaling on synaptic plasticity.

Spatial confinement
Diffusible molecules represent a major means of communication between cells. Cells release chemical messages into the extracellular space and these reach their targets by passive diffusion or by active transport (e.g. in the blood). The extent of influence of a released substance is determined by its concentration gradient and the sensitivity of its targets. This form of communication, however, does not permit discrimination between targets within the sphere of influence, just as a speaker before an audience cannot address one individual to the exclusion of the others.

Neurons have developed a way to select their targets, namely by approaching them with an axon and releasing the transmitter substance at the point of closest contact (as if two members of the audience were whispering into each other’s ears). This morphological configuration (the synapse) allows rapid and spatially confined action of the released substance, thus making neurons fast and precise communicators. The degree of spatial precision is impressive if one considers that subcellular membrane compartments as small as a fraction of 1 µm² (the postsynaptic density of a dendritic spine) can be selectively targeted by diffusible molecules [1]. The spatial confinement of these diffusible molecules is not absolute, however, as the compartment in which neurotransmitter is released, the synaptic cleft, forms a continuum with the extracellular space [1,2]. Thus, released neurotransmitter substances can potentially diffuse out of the cleft to also reach targets that are not juxtaposed. This escape of transmitter is mitigated by proteins responsible for the rapid degradation or sequestration of the released substances. For example, at CNS excitatory synapses, a glutamate molecule leaving the cleft is likely to be captured by specialized transporter proteins concentrated around the cleft on cell membranes of glia and neurons [3]. By acting as a sink, such transporters not only ensure the spatially restricted action of glutamate, but also might hasten the clearance of transmitter from the cleft, thus reducing the probability of rebinding to receptors or accumulation during repetitive release [4–9].

Escaping from the cleft

Do molecules of glutamate exiting the cleft ever escape sequestration by uptake proteins? And if so, what are the consequences? Immunohistochemical studies show that at least one class of receptors for glutamate, the metabotropic glutamate receptors (mGLURs), are located outside of the synaptic cleft and, hence, could represent potential targets for ‘escaping’ glutamate molecules [10,11]. These findings have been substantiated by physiological evidence indicating that released glutamate molecules can exit the synaptic cleft, elude glutamate transporters and bind to mGLURs [12–15]. Elucidation of the interplay between extrasynaptic receptors eagerly awaiting stray transmitter molecules and the transporters trying to restrict diffusional domains will now be necessary for a more complete comprehension of neuronal signaling.

Competing on the edge

A recent study by Gabor Brasnjo and Thomas Otis [16] provides a clear example of the interplay between extrasynaptic receptors and transporters at one of the numerically predominant excitatory synapses in the brain, the contact between granule cell axons (parallel fibers) and Purkinje cell dendrites in the cerebellar cortex. Neuronal glutamate transporters (nEAAT) expressed by Purkinje cells are located on the postsynaptic membrane surrounding the synaptic cleft [17]. Interestingly, mGLURs colocalize with glutamate transporters in this perisynaptic region [10]. This overlapping distribution suggests that the transporter proteins and mGLURs compete for glutamate molecules leaving the synaptic cleft (Fig. 1)

Brasnjo and Otis showed that when glutamate release occurred in response to a single action potential, uptake was clearly the winner in this competition (as no response to mGLUR activation could be recorded in Purkinje cells). By contrast, when glutamate release occurred in rapid succession during repetitive firing, mGLUR-mediated responses were readily detected, indicating that enough glutamate molecules had managed to