Solving the binding problem: cellular adhesive molecules and their control of the cortical quantum entangled network

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Abstract. Quantum entanglement is shown to be the only acceptable physical solution to the binding problem. The biological basis of interneuronal entanglement is described in the frames of the β-neurexin-neuroligin model developed by Georgiev (2002) and is proposed novel mechanism for control of the neurons that are temporarily entangled to produce every single conscious moment experienced as present. The model provides psychiatrists with 'deeper' understanding of the functioning of the psyche in normal and pathologic conditions.

The binding problem in psychology

How does the brain allow us to bind ideas together? Coming upon an object such as a rose, for example, one is able to correctly recognize it as a particular rose. But how do we recognize complex objects? It is well known that information in the brain is segmented; thus when one is confronted with the rose, the olfactory system (located in one region of the brain) recognizes the associated smell. The visual system (located in another region) takes the visual input stimuli and further segments them so as to recognize shapes and colours. Somehow, within the visual system, the shapes and colours come together, allowing us to recognize the form of the visual object. Further, the smell and the visual image are somehow able to fuse together, or bind, so that one is able to recognize the rose in its fullness from either component. How could this happen? This question is known as the binding problem. As Valerie Hardcastle has recently put it, "given what we know about the segregated nature of the brain and the relative absence of multi-modal association areas in the cortex, how [do] conscious percepts become unified into single perceptual units?" (Hardcastle, 1994).

The binding problem is not a new one; indeed it has over a century history. William James (1890) wrote:

> “In other words, no possible number of entities (call them as you like, whether forces, material particles, or mental elements) can sum themselves together. Each remains, in the sum, what it always was; and the sum itself exists only for a bystander who happens to overlook the units and to apprehend the sum as such; or else it exists in the shape of some other effect on an entity external to the sum itself. Let it not be objected that two H and O combine of themselves into ``water'' and henceforward exhibit new properties. They do not. The water is just the old atoms in the new position, H-O-H; the ``new properties'' are just their combined effects, when in this position, upon external media, such as our sense-organs and the various reagents on which water may exert its properties and be known”.

Anita Rado and Alwyn Scott (1996) try to resolve the binding problem using the Hebb's cell assembly theory introducing the notion of stable attractor. They suggest three steps to recognition: segmentation, binding, and association.

> “The easiest way to differentiate between these three components is to consider a visual perception problem. Consider the task of recognizing a pink circle. First, the brain segments the circle into at least two parts - colour and shape. The area of the visual system that recognizes colour labels the colour; the area of the visual system that recognizes shape labels the shape. Somehow, colour and shape are bound together into a cohesive mental object. The next step is association - searching in memory for objects that have appeared to be similar in form to the input - namely, a circle that is pink”.

Although their work is good in describing how brain cortex could search in the memory for already stored data this by no means explains how the present

experience in integrated into a whole! The example given by Rado & Scott (1996) just substitutes physical careers of information. If in a time moment there are excited two neurons – one for 'circle' and one for 'pink', and in the next moment is excited neuron that is 'pink circle', this replacement of the two excited neurons with one is not 'binding'. Following their logic we will come to the idea that in every moment only one neuron is responsible for our 'integrated' experience i.e. we should have enormous number of neurons ready to account for every possible experience! Because the number of our neurons is limited then obviously we should use only stored data. However, when person for first time experiences something and this could not be matched by something already stored in the memory the experience is still integrated. Or how we learn new things (not memorized yet) if we use the model of the stable attractor? In other words consciousness as phenomenon should not be identified with memory, no matter that the existence of consciousness without memorizing is 'tragedy' as seen in patients with severe both anterograde [1] and retrograde [2] amnesia. This means that 'binding' is not 'searching in the memory'.

Quantum entanglement could solve the binding problem

Quantum entanglement is a real phenomenon (Einstein called it "spooky action at a distance"), which has been demonstrated repeatedly through experimentation. Entanglement allows qubits (quantum bits) that are separated by incredible distances to interact with each other immediately, in a communication that is not limited to the speed of light. No matter how great the distance between the correlated particles, they will remain entangled as long as they are isolated. Particles, such as photons, electrons, or qubits that have interacted with each other retain a type of connection and can be entangled with each other in pairs, in the process known as correlation.

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[1] Anterograde amnesia – lack of capability (permanent or temporary) to remember events after certain time point

[2] Retrograde amnesia – loss of the memories before certain time point, usually before life-threatening incident

Knowing the spin state of one entangled particle - whether the direction of the spin is up or down - allows one to know that the spin of its mate is in the opposite direction. Even more amazing is the knowledge that, due to the phenomenon of superposition, the measured particle has no single spin direction before being measured, but is simultaneously in both a spin-up and spin-down state. The spin state of the particle being measured is decided at the time of measurement and communicated to the correlated particle, which simultaneously assumes the opposite spin direction to that of the measured particle.

Analysing the behaviour of two entangled quantum particles suggests us that they should have one integrated mind (consciousness). The observation that this 'integrated mind' has determined the output states of both particles proves that it is causally effective in choosing the output states, no matter that it has not initiated its own ψ-function collapse [3].

Split-brain experiments reveal that axons integrate conscious experience

The human nervous system (and the nervous systems of many other vertebrate species) has a bilateral symmetry most noticeable in the existence of the two cerebral hemispheres. The two halves of the brain, although exhibiting certain functional specializations, ordinarily work in an integrated manner to produce the conscious output of the nervous system, namely thought and action. Epilepsy is the general name given to a class of nervous system disorders involving convulsive activity of large numbers of nerve cells, and a classical surgical procedure in cases of severe epilepsy is section of the corpus callosum (commissurotomy), the large band of nerve fibers that serves as the primary connection between the two halves of the brain.

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[3] The collapse of the entangled state is initiated by the measuring process, the output states however are implicitly dependent on the decision of the quantum system itself i.e. "its mind". Whether the collapse is random process or non-computable decision of protoconscious quantum mind is still subject to discussion.

Roger Sperry and Ronald Myers first discovered the split-brain effect in the early 1960s. Myers (1955) showed that when the cat had its optic chiasm and corpus callosum severed, two independent learning centers were established - one in each hemisphere of the cat's brain. If the cat had its right eye open and its left eye covered and learned to make a simple conditioned response, it was unable to make the same response when the right eye was covered and the left eye was open. It was as if the learning was unable to be communicated to the other side of the brain; thus, it was obvious that information available to one side remained off-limits to the other.

Roger Sperry and Michael Gazzaniga (Gazzaniga & Sperry, 1967; Sperry & Gazzaniga, 1967; Sperry et al., 1969) began a series of studies of "split-brain" humans, patients who had had the corpus callosum severed as a therapeutic procedure, and the observations of these clinical patients have formed the basis for a number of significant ideas concerning brain function.

The World War II veteran (known in the scientific literature as W.J.) had undergone surgery to alleviate his epileptic seizures. After the surgery W.J. easily named and described colours, letters, and other information flashed briefly to the right side of his visual field; therefore, W.J.'s left hemisphere needed no help handling basic tasks requiring verbal responses. Then the scientists flashed items in W.J.'s left visual field and waited for the responses of his right hemisphere. As the anxious investigators looked on, W.J. acted as though he had suddenly gone blind. He insisted that he could not see bursts of light, boldface letters, or anything else presented to him. Yet his left hand, under the control of his right hemisphere, pushed down on a telegraph key each time a visual stimulus appeared, just as the scientists had instructed him to do.

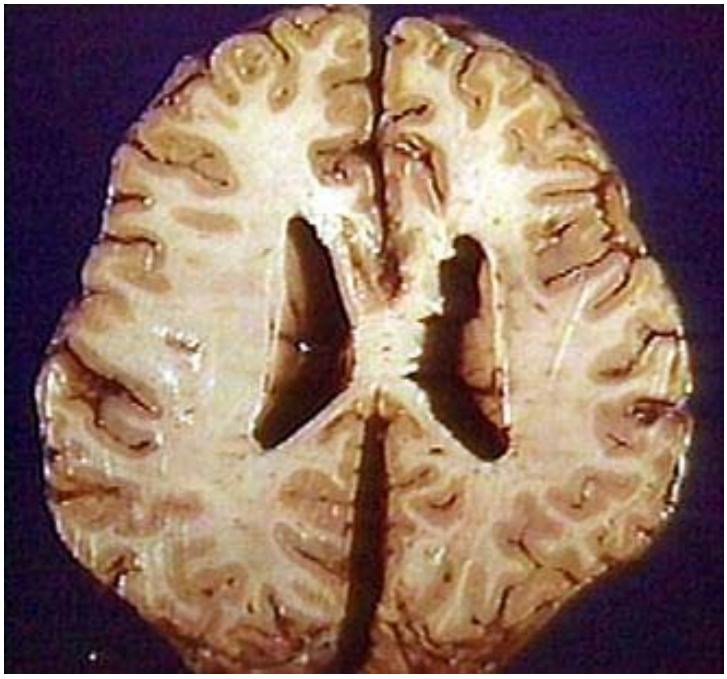

Figure 1 Brain, horizontal section through corpus callosum (white matter composed of myelinated axons seen here as X-shaped figure). *Image from Suzanne Stensaas and O.E. Millhouse, Digital Slice Of Life* http://medlib.med.utah.edu/kw/sol/sss/

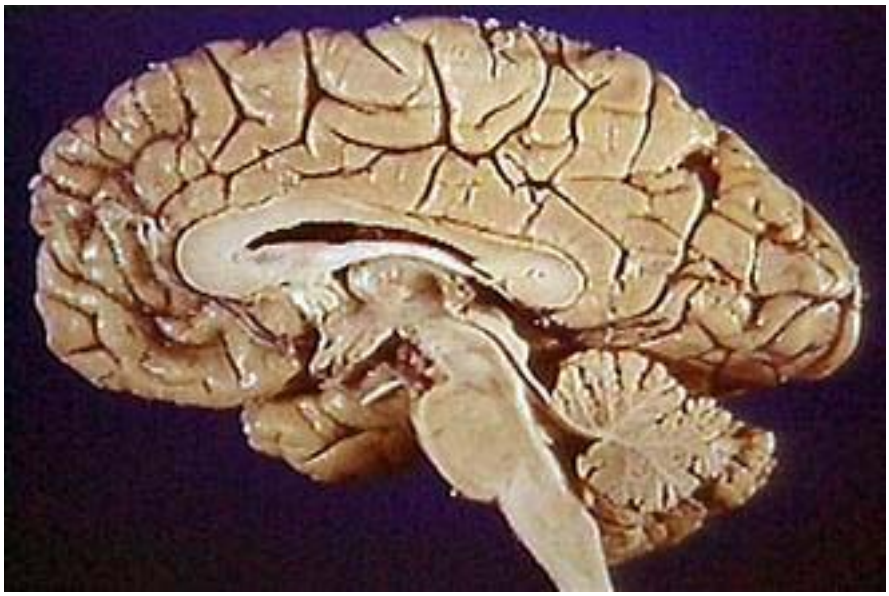

Figure 2 Midsagittal view of cerebrum. Corpus callosum (white matter composed of myelinated axons) is just beneath the cerebral giri. *Image from Suzanne Stensaas and O.E. Millhouse, Digital Slice Of Life* http://medlib.med.utah.edu/kw/sol/sss/

In his Nobel Lecture Sperry (1981) concluded that after commissurotomy “each of the disconnected hemispheres, not only the left, has its own higher gnostic functions. Each hemisphere in the lateralized testing procedures appeared to be using its own percepts, mental images, associations and ideas. As in the split-brain animal studies, each could be shown to have its own learning processes and its own separate chain of memories, all of course, essentially inaccessible to conscious experience of the other hemisphere”. That is after commissurotomy the human brain hosts not one but two minds (or more)!

New Developments in Split Brain Surgery

Until recently it has been believed that the entire corpus callosum must be severed to provide proper relief from the severe epilepsy the surgery was trying to negate. However this is not necessarily the case, the corpus callosum might be able to be severed enough to provide relief, without losing all neural integration.

Dr. H. G. Gordon, a neurobiologist at the California Institute of Technology says the connections at the back of the brain alone are enough to integrate both human hemispheres. Speaking for a California research team, he reported a new form of surgery, devised by P. J. Vogel of Los Angeles, which stops seizures completely, or at least renders them treatable with drugs. At the same time, he added:

> "Psychological tests of Vogel's patients yield results identical to those of normal subjects. We conclude, the cerebral hemispheres totally integrate if but a small fraction of the corpus callosum remains intact. "

In Vogel's new operation (called anterior cerebral commissurotomy) the surgeon opens the skull, lays back the brain's coverings and, with a tool called a cerebral retractor, exposes the corpus callosum between the two hemispheres. Then he snips through the front three-fourths of the corpus

callosum and, while at it, also severs a pipe-cleaner-sized cross connection known as the anterior commissure. But the back of the corpus callosum -- the splenium -- he leaves intact.

The splenium of the corpus callosum has been found to be the dominant path of the visual aspects of hemispheric integration. Whereas the genus has been found to control motor aspects. For this new procedure, the motor aspects much more pertinent to epilepsy seizures, are severed, while the splenium, the center of visual cross over, remain intact. This would make the procedure required for severe epilepsy much safer and more practical. The patient would be relieved of the extreme seizures, while retaining interhemisphereic visual pathways and some other communication between hemispheres.

This procedure is now widely used in place of the complete corpus commissurotomy, and experiments are being done with exactly how much of the brain needs commissured. The procedure doesn't perfectly integrate the two hemispheres; it has been found that callosal transfer times are significantly slower after the operation has occurred. This is thought to be because visual transfer time across the corpus is slower then the motor transfer time. Also bimanual coordination is thought to be somewhat inhibited by this procedure. Never the less, there is definite progress over the complete loss of communication which was thought to happen in the original split brain subjects.

The split-brain experiments reveal that axons are essential for conscious experience integration, suggesting that the key towards understanding the neuromolecular basis of ‘conscious binding’ should come from investigation of the axo-dendritic synapses. Also it comes out that if a partial communication between the two hemispheres is left the experience could still be integrated!

The CNS synapse

The most common type of synapse joins a pre-synaptic axon terminal and a postsynaptic dendrite across a gap, the synaptic cleft, which measures between 20–30 nm. The synaptic cleft is slightly wider than the gap between adjacent apposed membranes and is filled with an amorphous, electron-dense material. The pre- and postsynaptic membranes appear thicker than the surrounding plasmalemma owing to varying amounts of dense material attached to the cytoplasmic faces on either side of the synapse. Presynaptic terminals are filled with synaptic vesicles containing neurotransmitters – glutamate, at most excitatory synapses, and gamma-aminobutyric acid (GABA) or glycine at most inhibitory synapses. A subpopulation of vesicles is docked at the membrane and ready to fuse and release neurotransmitters, thus defining the 'active zone'.

Astrocytic processes are observed at the perimeter of synapses, but the extent to which they surround the active zone varies substantially (Palay & Chan-Palay, 1976; Ventura & Harris, 1999). While the synapse is highly specialized for inter-cellular signalling, it is also an adhesive junction, having many of the properties associated with other cell–cell junctions. In appearance, the CNS synapse is most closely related to the adherens junction between epithelial cells. The junctions span similar membrane distances; fuzzy, electron-dense material fills the intermembrane zones; and both contain cadherins, a family of Ca^{2+} - dependent cellular adhesive molecules (CAMs). The principal difference between these two junctional types is that adherens junctions are functionally symmetric, joining identical cell types across the same cellular domains, whereas synapses are polarized, most often joining functionally distinct cellular domains: axon to dendrite or soma.

Several types of CAMs have been localized to CNS synapses, most of which fall into four groups (Benson et al., 2000): [1] integrins, [2] immunoglobulin superfamily, [3] cadherins and [4] neurexins and neuroligins.

Integrins

Integrins are heterodimeric glycoproteins comprising two noncovalently associated subunits, α and β. Each α and β subunit contains a large extracellular domain, a transmembrane domain, and a cytoplasmic domain that interacts with actin via talin, α-actinin or vinculin and numerous cytoplasmic signalling molecules. The extracellular domains of both subunits form the ligand-binding site, which, for many integrins, recognizes a sequence – Arg-Gly-Asp (RGD) – found in many matrix proteins. Integrins require divalent cations for ligand binding, and their activity can be regulated by cytokines, agonists or cations. Although the classic integrin interaction is to join cells with substrates, integrins can also function in cell–cell adhesion through immunoglobulin (Ig) superfamily members or cadherins. More than ten different integrin subunits are expressed in the brain and are differentially localized. Electron microscopy has shown that $\alpha 8$ and $\beta 8$ are concentrated at some post-synaptic densities.

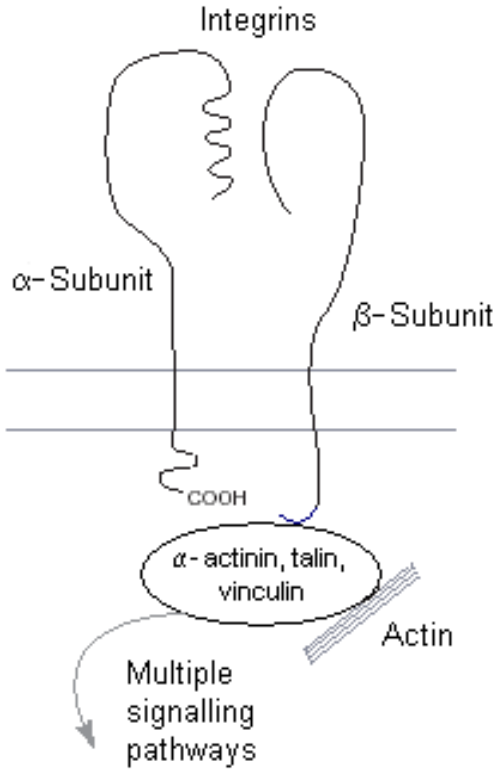

Figure 3 Structure of integrins.

Immunoglobulin (Ig) superfamily

Ig superfamily members are either type I or GPI-linked membrane proteins having one or more Ig-like domains that mediate recognition and adhesion, and usually one or more fibronectin III repeats. Most members have preferences for homophilic or heterophilic interactions, but many can engage in both, and the strength of adhesion varies widely. The cytoplasmic domains of some can be tethered to actin and are essential for signal transduction. Some members, particularly NCAM, fasciclin II (Drosophila) and L1 are required for aspects of axonal guidance and cell migration during development. NCAM exists in a variety of differentially spliced and glycosylated isoforms. In adult brains, at least one NCAM isoform becomes concentrated in some dendritic spines.

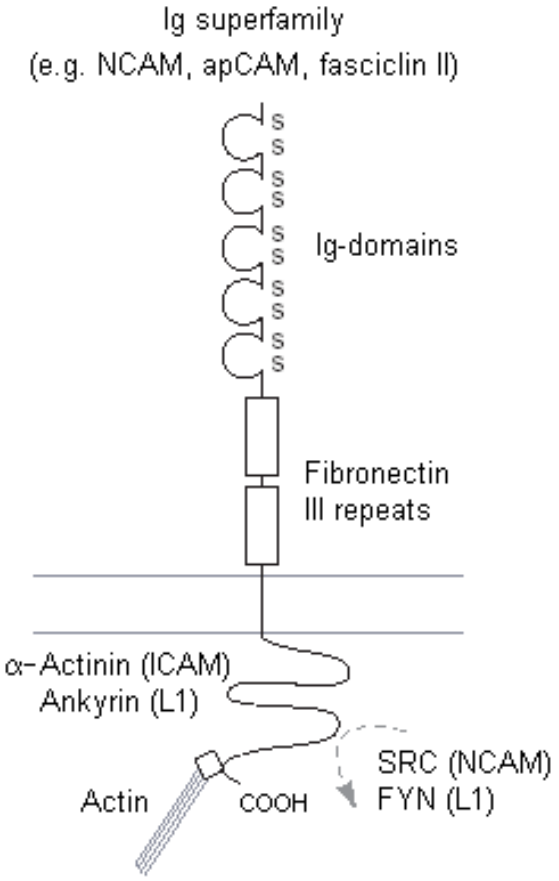

Figure 4 Structure of immunoglobulin family adhesive proteins.

Cadherins

The cadherin superfamily includes classic cadherins, cadherin-like neuronal receptors (CNRs) and protocadherins. All are proteins with a single transmembrane domain mediating strong, Ca^{2+} -dependent cell–cell adhesion via the first of five or six tandemly repeated domains. Most interactions are homophilic, but closely related cadherins can form cis-heterodimers within the plane of the membrane as well as engage in trans-heterophilic interactions across membranes or can bind other cell-adhesion molecules. For classic cadherins, strength of adhesion is modulated by the cytoplasmic tail through regulation of lateral clustering by interactions with p120 and δ-catenin, and through linkage to actin via α-, β- and γ-catenin. The CNRs are linked to the tyrosine kinase fyn. A majority of synapses in the CNS contain cadherins, and different cadherins have been localized at mutually exclusive synaptic loci in the CNS.

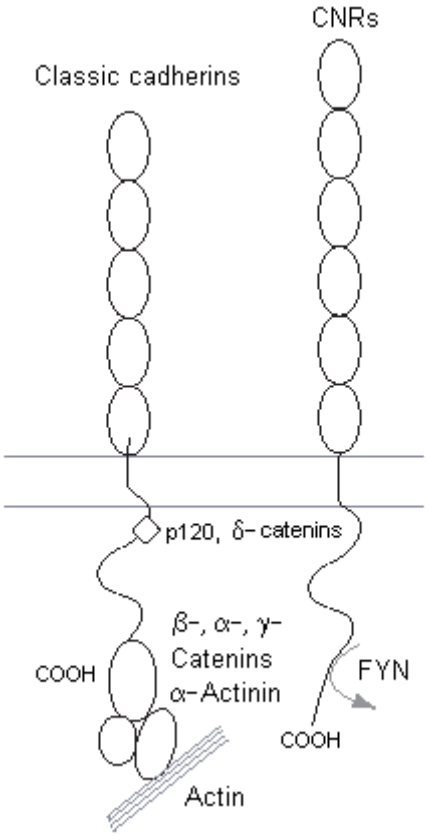

Figure 5 Structure of cadherins and cadherin-like neuronal receptors (CNRs).

Neurexins and neuroligins

Neurexins are a family of brain-specific proteins that can be differentially spliced to produce an enormous variety of molecules. α- and β-neurexins are presynaptic; only β-neurexins have an identified postsynaptic ligand, the neuroligins. Neuroligins 1–3 are type I membrane proteins that bind to neurexins in a Ca^{2+} -dependent manner through their extracellular N-terminal domain, which is homologous to serine esterases but lacks catalytic activity. Neurexins and neuroligins would be well situated to link pre- and postsynaptic signalling mechanisms: the intracellular C-terminus of neuroligins binds to the PDZ-containing protein PSD-95, which is thought to function as a nexus for clustering receptors and signalling molecules at the postsynaptic side of the synapse, whereas the C-terminus of neurexins binds to CASK, another PDZ-containing protein found presynaptically.

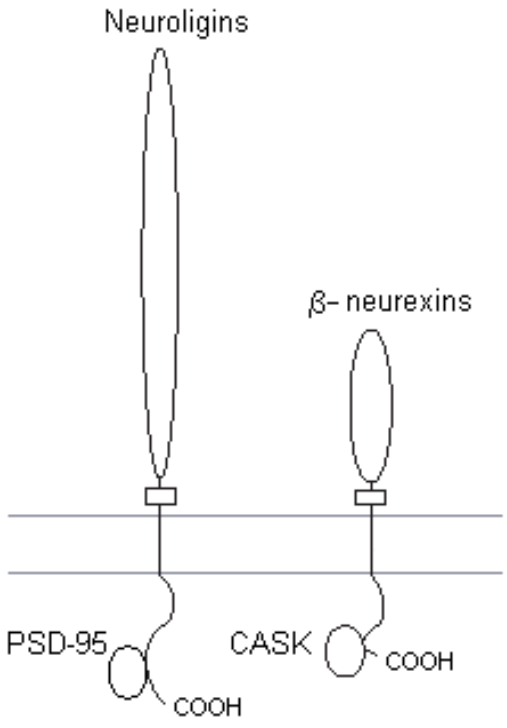

Figure 6 Structure of β-neurexins and neuroligins.

The intrasynaptic β-neurexin–neuroligin-1 adhesion could mediate interneuronal entanglement

In the model developed by Georgiev (2002) the neuronal cytoskeletons are the main structures processing the incoming in the brain cortex information and sustaining macroscopic long-range quantum coherence. However essentially arises the question how the coherence is sustained between the individual neurons, and as we have seen from the split-brain experiments the coherence should be spread across the axo-dendritic synapses!

Ultrastructural studies of excitatory synapses have revealed an electron-dense thickening in the postsynaptic membrane - the postsynaptic density (PSD). The PSD has been proposed to be a protein lattice that localizes and organizes the various receptors, ion channels, kinases, phosphatases and signaling molecules at the synapse (Fanning & Anderson, 1999). Studies from many laboratories over the past ten years have identified various novel proteins that make up the PSD. Many of these proteins contain PDZ domains, short sequences named after the proteins in which these sequence motifs were originally identified (PSD-95, Discs-large, Zona occludens-1). PDZ domains are protein–protein interaction motifs that bind to short amino-acid sequences at the carboxyl termini of membrane proteins. These PDZ domain-containing proteins have been shown to bind many types of synaptic proteins, including all three classes of ionotropic glutamate receptors, and seem to link these proteins together to organize and regulate the complex lattice of proteins at the excitatory synapse.

CASK (presynaptic) and PSD-95 (postsynaptic) stabilize synaptic structure by mediating interactions with cell adhesion molecules neurexin (presynaptic) and neuroligin (presynaptic) or by indirectly linking synaptic proteins to the cytoskeleton through the actin binding protein 4.1 or the microtubule-binding protein CRIPT.

The third PDZ domain in PSD-95 (and PSD-93 and PSD-102) has been demonstrated to bind to the carboxy-terminal tail of neuroligins (Irie et al., 1997) and CASK binds to the cell surface protein neurexin (Hata et al., 1996). Direct binding of neurexins to neuroligins has been demonstrated to promote cell–cell interactions, leading to the suggestion that adhesive interactions mediated by PDZ proteins might promote assembly or stabilization of synaptic structure. The CASK PDZ domain has also been shown to bind to syndecans (syndecan-2), which are cell surface proteoglycans implicated in extracellular matrix attachment and growth factor signalling.

The organization of membrane domains might also be mediated by the ability of many of these multidomain proteins to promote direct or indirect linkage to cytoskeleton. CASK is tethered to the cortical cytoskeleton by the actin/spectrin-binding protein 4.1. The third PDZ domain of PSD-95 has been demonstrated to bind to the protein CRIPT, which can recruit PSD-95 to cellular microtubules in a heterologous cell assay. Linkage of these scaffolding proteins to the cytoskeleton might help to stabilize their associated transmembrane proteins within discrete plasma membrane domains.

We have considered the molecular organization of the synapse to reveal the molecular connection between the two neuronal cytoskeletons. It is not surprise that the intrasynaptic β-neurexin-neuroligin-1 adhesion that is central for synapse formation, not only organizes the pre- and post- synaptic architecture but also could mediate interneuronal entanglement. The entangled cytoskeletons then could act as 'unity' or 'holograph'. The 'holograph' can be defined as object/subject such that every part of it contains all the information possessed by the whole. The "whole in every part" nature of a hologram provides us with an entirely new way of understanding organization and order. If we try to take apart something constructed holographically, we will not get the pieces of which it is made; we will only get smaller wholes.

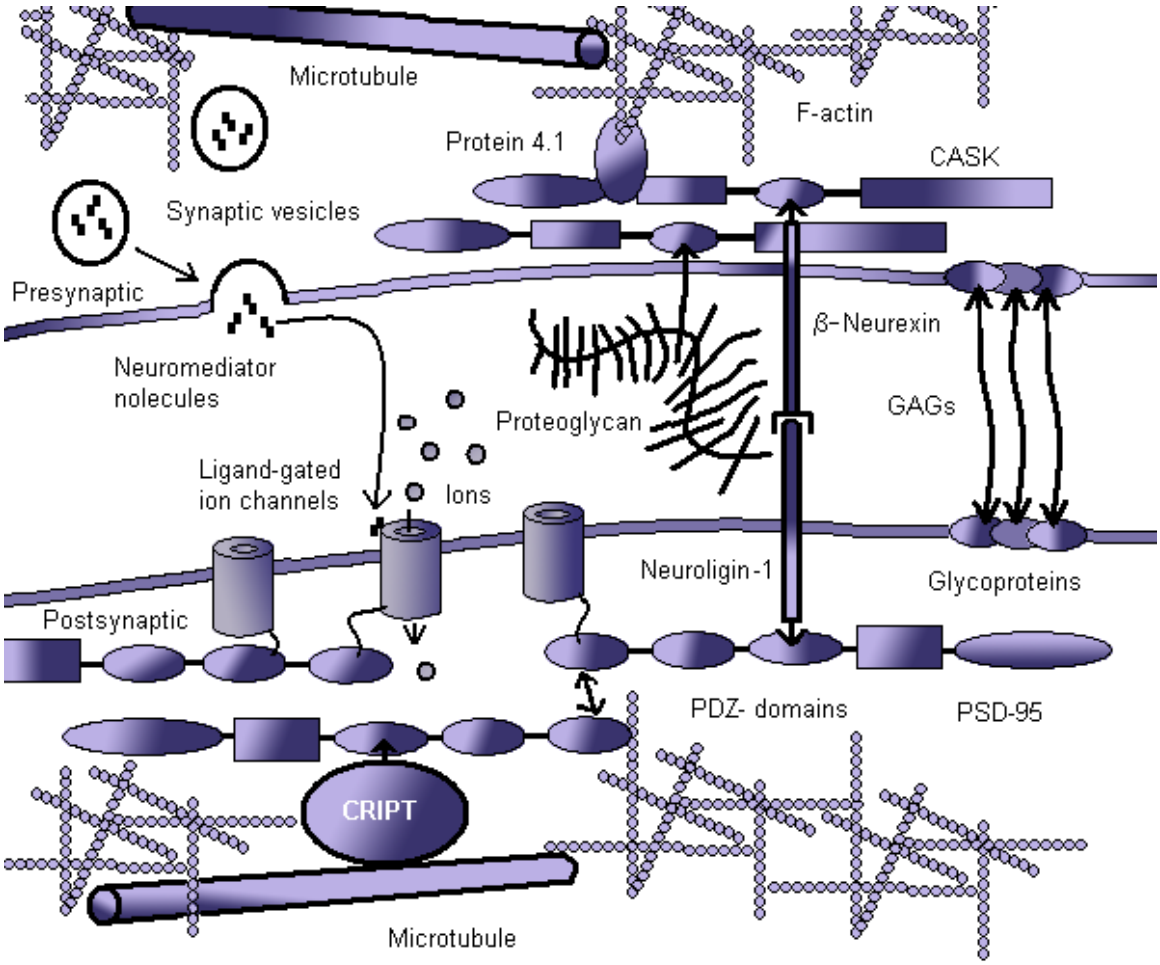

Figure 7 The β-neurexin-neuroligin-1 adhesion could influence the cytoskeletons of the two neurons. The quantum coherence between neurons is mediated by β-neurexin-neuroligin adhesion, which can be shielded by proteoglycans (syndecan-2, phosphacan) or glycosaminoglycans (GAGs) [4] from decoherence.

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[4] The synaptic cleft is filled with an amorphous, electron-dense material, as revealed by electron microscopy studies. The main constituents of this electron-dense substance are glycosaminoglycans and proteoglycans! The glysocaminoglycan molecules project negative SO_3 groups thus repelling the chloride ions that are known to disturb the dynamical order of water molecules. The water molecule ordering is essential mechanism for shielding the coherent quantum states inside the neuronal cytoplasm as shown by Stuart Hameroff, Jack Tuszynski and Scott Hagan in a recent paper (Hagan et al., 2000). The dynamical water molecule ordering is modelled in the papers of Mari Jibu and Kunio Yasue that suggest biological importance of two quantum phenomena: superradiance and self-induced transparency occurring in the coherent water.

CAMs modulate short- and long-lasting forms of synaptic plasticity

After seeing how neurons could sustain interneuronal coherence essentially arises the question is there any biological mechanism that serves as regulator of the neurons that are currently entangled into the coherent quantum network, ensemble called with the exotic name 'hyperneuron' (Woolf & Hameroff, 2001).

At least two temporally and mechanistically distinct processes contribute to activity-dependent synaptic plasticity, which lasts from tens of minutes to hours or more. Short-lasting forms of synaptic plasticity can be induced quite rapidly, do not require protein synthesis, and are not sustained beyond a few hours. Such rapidly induced, but short-lasting, forms of synaptic plasticity probably reflect changes in the strength of pre-existing synapses through posttranslational modifications and translocation of pre- and postsynaptic proteins (Malenka & Nicoll, 1999). By contrast, long-lasting changes in synaptic strength, ones that might endure for several hours to days, require gene transcription and protein synthesis. Such long-lasting forms of synaptic plasticity can be associated with structural remodelling of synaptic architecture and the formation of new synaptic contacts (Bailey, & Kandel, 1993). There is growing evidence that CAMs play important roles in modulating both short-lasting synaptic plasticity at pre-existing synapses and long-lasting synaptic plasticity in which synaptic structural changes and new synapse formation can also occur.

In the mammalian brain, the contribution of CAMs to synaptic plasticity has been studied mostly in the context of long-term potentiation (LTP). LTP can be induced at many different types of synapses throughout the brain (Bennett, 2000) but is best characterized in living brain-slice preparations of the hippocampus, a structure crucial for memory formation (Squire, 1992). When brief, high frequency trains of stimuli (tetanizing stimuli) are used to excite a neuron; a rapid-onset, short-lasting form of LTP (lasting 1–2 h) is induced that does not require protein synthesis. This form is called early (E)-LTP and very

likely involves rapid changes in the strength of pre-existing synapses (Malenka & Nicoll, 1999). By contrast, when multiple, widely spaced trains of high-frequency stimuli are used, both E-LTP and a subsequently developing, longer-lasting form of LTP (L-LTP) are induced, the latter lasting several hours to days or more. L-LTP requires gene transcription and protein synthesis and has been associated with growth of new dendritic spines (Engert & Bonhoeffer, 1999) and formation of new synapses (Toni et al., 1999). Each of the major families of CAMs has been shown to play a role in the induction or maintenance of E- and/or L-LTP.

Adhesion proteins modulate E-LTP at pre-existing synapses

Classic cadherins (N- and E-cadherin), a cadherin-like protein (arcadlin) and some CAMs of the Ig superfamily (NCAM, L1 and telencephalin) have been shown to play a role in the induction of E-LTP (Luthi et al., 1994; Muller et al., 1996; Tang et al., 1998; Sakurai et al., 1998; Yamagata et al., 1999). When hippocampal slices are pretreated with function-blocking antibodies against adhesion proteins, synthetic blocking peptides or recombinant protein fragments, LTP either fails to develop or the posttetanic potentiation decreases rapidly back to baseline. Exposure to such blocking reagents generally does not affect basal synaptic properties, although antibodies to arcadlin reduce normal synaptic transmission as well as prevent LTP (Yamagata et al., 1999). Thus, the data suggest that these adhesion proteins contribute to the earliest mechanisms leading to enhanced synaptic strength. When blocking antibodies or peptides are applied 10–30 minutes after LTP induction, there are no further effects on synaptic strength. This could either reflect a specific role limited to the earliest phases of LTP or that the blocking reagents become ineffective in attenuating E-LTP after it is established because of changes in the conformation or accessibility of the adhesion proteins.

A role for NCAM in LTP induction suggested by NCAM antibody-blocking experiments (Luthi et al., 1994) is corroborated by studies showing an inability to induce LTP in area CA1 after enzymatic removal of the polysialic acid (PSA) that is attached to certain isoforms of NCAM (PSA-NCAM) or in transgenic mice carrying a targeted deletion of the gene encoding NCAM (Muller et al., 1996). These studies have raised the question of whether LTP in area CA1 depends mostly on PSA, rather than on NCAM *per se*. Additionally, NCAM-deficient mice also exhibit a decrease in the magnitude of LTP in area CA3 elicited by stimulation of mossy fibres (Cremer et al., 1998), although other studies have failed to find any differences in LTP between wild type and NCAM-deficient mice (Holst et al., 1998). Because NCAM-deficient mice display marked developmental abnormalities in the morphology and distribution of the presynaptic mossy fibre terminals (Cremer et al., 1997; Seki & Rutishauser, 1998), an additional question has been raised as to whether the impaired area CA3 LTP in NCAM-deficient mice simply reflects abnormal development of the presynaptic input. However, a recent study has clarified both the roles of NCAM and PSA in LTP and the issue of whether NCAM is directly involved in synaptic plasticity or indirectly affects LTP in area CA3 through its important role in development of this brain region. Eckhardt et al. (2000) engineered transgenic mice carrying a targeted deletion of the gene encoding one of two identified polysialyl-transferases that are responsible for attaching PSA to NCAM. Their study established that in area CA1, PSA plays an essential role in LTP, whereas, in area CA3, NCAM, but not PSA, appears to be essential for LTP.

Integrin-mediated adhesion, by contrast, plays a role in the early stabilization of E-LTP but little or no role in its induction. Disrupting integrin-mediated adhesion by exposing hippocampal slices to antagonistic peptides containing the integrin recognition sequence Arg-Gly-Asp (RGD) up to 10 min following induction of E-LTP causes a gradual decay in synaptic strength over a ~40 min period, without affecting the initial establishment of E-LTP (Staubli et al., 1998). Agonist-activated intracellular signalling pathways that cause a conformational change in the integrins to allow high-affinity binding, for

example, might alter the adhesive binding affinity of integrins. In a resting state integrins could exists in a low-affinity state unable to bind to their ligands. After activation (by agonists), integrins undergo a conformational change to a high-affinity state binding to their ligands. Ligand binding can also be regulated by integrin clustering (avidity modulation).

A recent study has shown that N-cadherin and L1 are physically associated with NMDA-type glutamate receptors in large, multiprotein complexes isolated from mouse brain (Husi et al., 2000). Since NMDA receptors are required for LTP induction (Malenka & Nicoll, 1999), this important finding supports the possibility of a direct link between NMDA receptor activation during LTP induction and modulation of adhesion protein function at the synapse. For example, one consequence of a physical–functional linking is that NMDA receptor-mediated synaptic activity during the induction of LTP might rapidly alter the strength of the adhesive force that maintains apposition between pre- and postsynaptic membranes or between neuronal and surrounding glial membranes. Tanaka et al. (2000) showed that strong depolarization of cultured hippocampal neurons by treatment with either high concentrations of K^+, the glutamate receptor agonist NMDA or the spider toxin α-latrotoxin causes synaptically localized N-cadherin to dimerize and acquire resistance to degradation by proteases, two molecular changes that, in other systems, are well-established indices of augmented and stable adhesive force (Brieher et al., 1996; Tamura et al., 1998). These molecular changes to N-cadherin are prevented when neurons are stimulated in the presence of APV, an NMDA receptor antagonist. Since in the study of Tanaka et al. (2000) the neurons were grown and maintained in the absence of direct contact with glial cells, the data indicate that NMDA receptor-mediated synaptic activity augments the cadherin-mediated adhesive force that holds pre- and post-synaptic membranes in apposition.

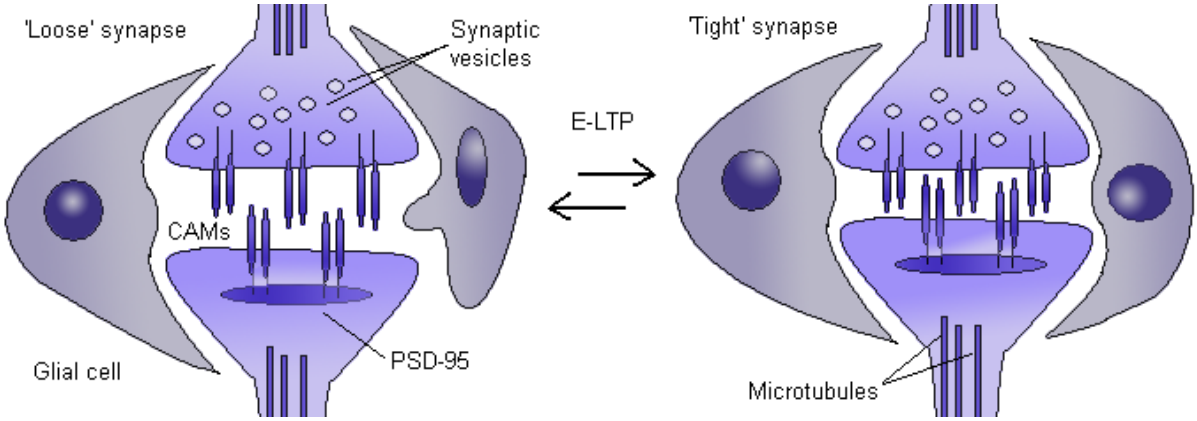

Figure 8 Early-long term potentiation (E-LTP) after tetanizing stimulation.

How could activity-induced changes in adhesive strength affect synaptic physiology? There are several classical possibilities:

- Adhesion proteins might, in turn, directly modulate glutamate receptor channel properties, a possibility suggested by the physical association of N-cadherin and L1 with NMDA receptors in large, multiprotein complexes. This would place adhesion molecules directly in the initial signalling events responsible for LTP.
- The distance between pre- and postsynaptic membranes (the synaptic cleft) might be altered. This could affect the cleft glutamate concentration, which is increased at potentiated synapses (Choi et al., 2000).
- The size of the apposed active zones in the pre- and postsynaptic membranes might be altered. This could affect the density, compartmentation or composition of postsynaptic glutamate receptors (Shi et al., 1999; McAllister & Stevens, 2000).
- The extent to which glial cell (astrocyte) processes surround the edges of the synapse might be altered by changes in the strength of adhesion between neuronal and glial membranes (Wenzel et al., 1991). This could modify the rate of glutamate reuptake from the synaptic cleft by affecting the density or proximity of glutamate transporters, which are localized predominantly to the perisynaptic astrocytic processes (Conti & Weinberg, 1999).

- Altered ‘outside-in’ signalling by adhesion proteins could produce rapid effects on other signalling pathways. Integrin clustering, for example, leads to tyrosine phosphorylation of a variety of proteins. Although integrin cytoplasmic tails lack endogenous kinase activity, they interact with a number of proteins [e.g. focal-adhesion kinase (FAK), paxillin, integrin-linked kinase (ILK)], which in turn interact with many classic signalling pathways such as mitogen-activated protein kinase (MAPK), Rho and protein kinase C (Clark & Brugge, 1995). In addition, many adhesion proteins can associate with other transmembrane or membrane- associated proteins. For example, recent studies show that the deficient LTP observed in hippocampal slices prepared from NCAM-knock-out mice can be rescued by exogenous application of brain-derived neurotrophic factor (BDNF), suggesting crosstalk between NCAM and growth-factor related signalling (Muller et al., 2000).

Quantum possibility in the brain cortex:

- Altering the distance between the two neural membranes may act as switch for the β-neurexin-neuroligin interneuronal spreading of coherence. The microenvironment of the β-neurexin-neuroligin link is altered thus affecting its shielding against decoherence. Possible switches between ‘active’ and ‘inactive’ states are also observed reflecting the possibility neuroligin EF-hand motifs to bind Ca^{2+} ions, altering their interaction with β-neurexins (Tsigelny et al., 2000). Thus essential link between the electromagnetic stimulation of the neuron, its synaptic activity and its capacity to get entangled with other cortical neurons is established! The control of the neurons currently entangled in a giant quantum network called ‘hyperneuron’ at psychological level indeed will control the ‘concepts’, ‘perceptions’ or ‘ideas’ that are bound into an integrated ‘conscious present’. Thus the ‘binding problem’ could be solved via control of the interneuronal quantum entanglement at the neuromolecular level.

Long-lasting forms of synaptic plasticity

Formation of new synaptic sites as well as the loss of old ones occurs throughout life and represents another aspect of synaptic plasticity in which synaptic communication is modified for long-term periods. What are the proteins that enable new synapse assembly in the mature brain to ensure that pre- and postsynaptic membranes link-up appropriately, stabilize and become functional? Synaptic adhesion proteins are of particular interest in this context because pre- to postsynaptic membrane adhesion is one of the initial events in the construction of a synaptic junction during brain development and remains a fundamental component of the maintenance of synapses in maturity. Thus, the molecular adhesive machinery required for synapse assembly in development would be expected to have an essential role in modulating synaptic architecture in the context of plasticity-related structural remodelling.

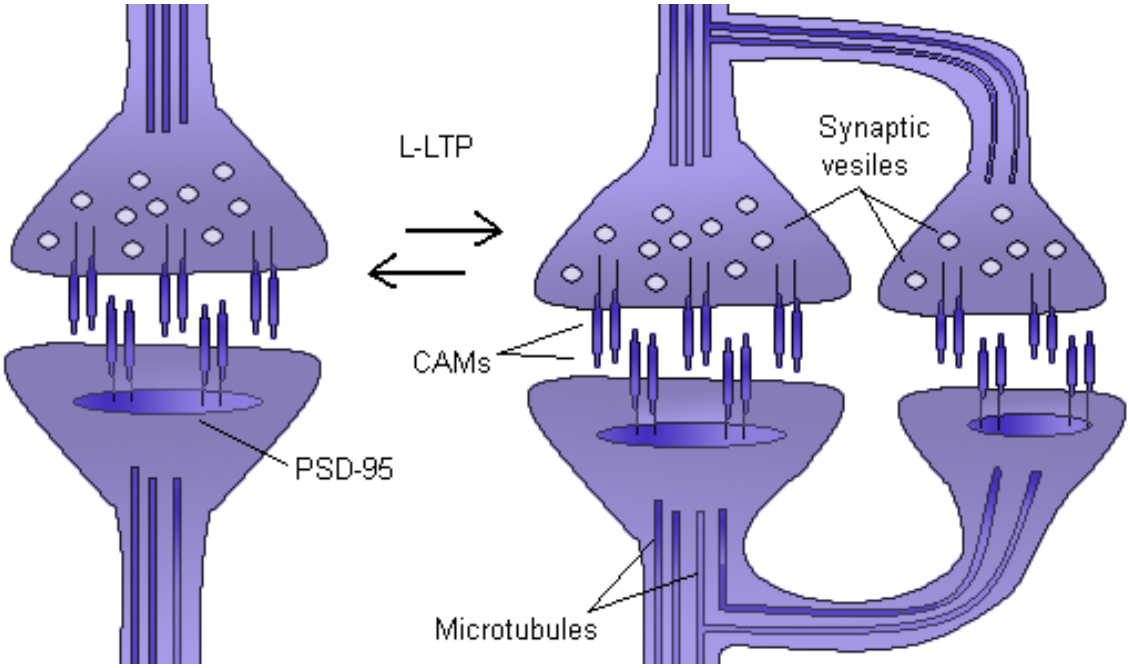

Figure 9 Long-term plasticity (L-LTP). The presynaptic neuron extends axonal projections and forms new synapses.

Other forms of long-lasting synaptic plasticity could involve changes in adhesion between perisynaptic neuronal membranes and the normally contiguous glial cell membranes that wrap around the synapse. In the hypothalamus was shown that glial processes form a reversible barrier to synaptic communication, presumably enabled by changing levels of neuronal-glial membrane adhesion.

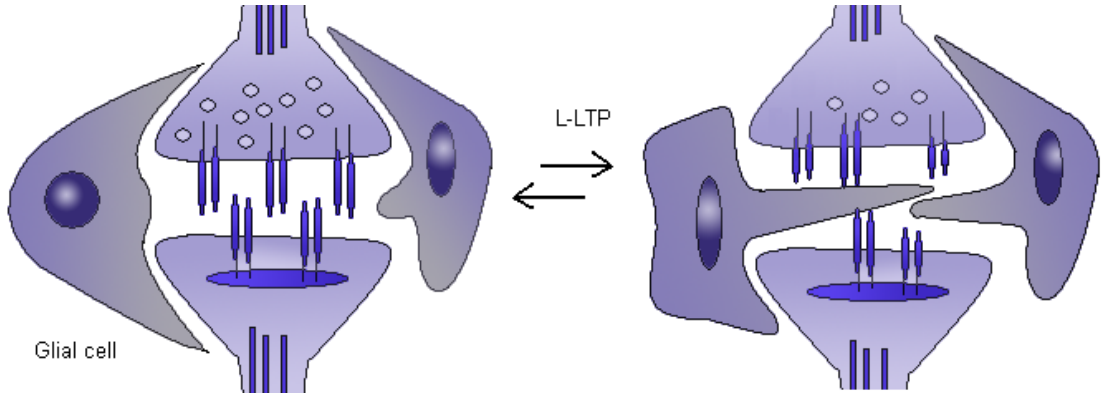

Figure 10 Long-term synaptic plasticity: reversible glial cell barrier at active synapses.

Perturbing the function of CAMs affects learning and memory

The importance of CAMs to synaptic function and plasticity is underscored by the behavioural deficits in learning and memory that result from altering cell-adhesion function. In Drosophila, Grotewiel et al. (1998) identified a gene locus linked to the memory mutant Volado, which encodes two isoforms of a member of the α-integrin subunit family. The protein products encoded by Volado are enriched in the neuropil of the mushroom body, a brain region important for learning in insects. Volado mutants have impairments in olfactory memories. The impairment is rescued by conditional expression of a Volado transgene, indicating a crucial role for the integrins in the processes underlying the formation of olfactory memories. The histological analyses of the brains of the Volado mutants suggest normal neuronal architecture, raising the possibility that impaired integrin signalling, rather than overt synaptic structural changes, might be responsible for the memory impairment.

Altering L1 and NCAM function affects learning and memory both at an early, acquisition phase and in a later, memory-consolidation phase. Transgenic mice engineered so that their astrocytes express L1 ectopically, learn the position of a hidden platform faster than control mice when tested in the Morris water maze (Wolfer et al., 1998), a test of spatial memory. By contrast, NCAM-knockout mice show impaired spatial learning when tested in the Morris water maze (Cremer et al., 1994), while similar deficits in spatial learning are evident in rats following enzymatic removal of sialic acid from PSA-NCAM (Becker et al., 1996).

In other studies, memory retention in chicks is impaired 24 h following a visual categorization task when antibodies against L1 are injected intracranially at any one of three restricted time-periods: before, 5.5 h after and 15–18 h after training (Tiunova et al., 1998). Similarly, intraventricular injections of antibodies against NCAM ~6–8 h following passive avoidance training in chicks (Scholey et al., 1993) or rats (Doyle et al., 1992a) impairs retention of the avoidance response but is without effect if injected during the training period. In these tasks, the level of polysialylation of NCAM increases over a period of hours following training in rats (Doyle et al., 1992b), suggesting that NCAM gradually acquires a less-adhesive state in order to promote structural remodelling (Rutishauser & Landmesser, 1996). Perhaps the antibodies against NCAM impede polysialylation and thereby prohibit potential structural changes in synaptic architecture required for retention of the avoidance response. It should be emphasized, however, that the precise mechanistic links between altered adhesion protein function and enhanced or diminished behavioural learning are unknown [5].

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[5] CAMs are essential for learning and memory storage, however the mechanism of their action is still unknown. The classical neuroscience tries to link CAM function to subneuronal effects therefore implying that consciousness can't be explained *per se* by the neuronal membrane firing! In the proposed quantum switching in and out of the 'hyperneuron' memory impairment could be secondary result from improper conscious image processing and integration.

Discussion

The proposed neuromolecular model for regulation of the switching in and out of the quantum coherent network in the brain cortex is the first ever done trial to explore this issue. The mechanism is based on experimental data collected by numerous researchers, so it could be regarded as 'evidence based'. The model has possible applications in the analysis of normal and pathological mental conditions and could provide physicians with 'deeper' understanding of how mind functions. For example, dreaming could be regarded as a function of 'randomly entangled' cortical neurons without memorizing of the experience. It is well known that only if person wakes up during REM sleep he/she could provide partial memories about the dream and these memories disappear too fast in a rate that one hardly could remember the content of its own dream, no matter that he consciously wants to. Dreaming is associated with low frequency EEG rhythms (1-4 Hz under deep sleep, δ-waves), so obviously there is not enough synaptic activity to 'tighten' the synaptic clefts (switching in the individual neurons) [6].

Under certain pathological conditions there is 'splitting' of the psyche, so that one's brain hosts two or more characters or 'persons' that differ too much from each other; and there could be unexpected switches between these two. All these states could be well explained with disturbances in the control of the quantum entangled cortical network.

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[6] It was already outlined that the transition between 'loose' and 'tight' synaptic cleft in early-LTP controlled by synaptic CAMs is prerequisite for β-neurexin-neuroligin switching in and out of the giant quantum coherent network composed of brain cortical neurons called 'hyperneuron'. The calcium ion binding by neuroligins, the microenvironment (proteoglycans, GAGs, glycoproteins, water molecule ordering) etc. further contribute to the precise control of the β-neurexin-neuroligin switch!

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