Interneuronal macroscopic quantum coherence in the brain cortex! The role of the intrasynaptic adhesive proteins β-neurexin and neuroligin-1

Danko Dimchev Georgiev, Medical University Of Varna, Bulgaria
E-mail: dankomed@softhome.net

There are many blank areas in understanding the brain dynamics and especially how it gives rise to consciousness. Quantum mechanics is believed to be capable of explaining the enigma of conscious experience, however till now there is not good enough model considering both the data from clinical neurology and having some explanatory power! In this paper is presented a novel model in defence of macroscopic quantum events within and between neural cells. The β-neurexin-neuroligin-1 link is claimed to be not just the core of the central neural synapse, instead it is a device mediating entanglement between the cytoskeletons of the cortical neurons. Thus a macroscopic quantum state can extend throughout large brain cortical areas and the subsequent collapse of the wavefunction could affect simultaneously the subneuronal events in millions of neurons. The β−neurexin-neuroligin-1 complex also controls the process of exocytosis and provides an interesting and simple mechanism for retrograde signalling during learning-dependent changes in synaptic connectivity.

1. Subneuronal macroscopic long-range quantum effects

There are a couple of models trying to resolve the enigmatic feature of consciousness. The most popular is the Orch OR model (Hameroff & Penrose, 1996a; 1996b) supposing that the microtubule network within neurons acts like a quantum computer. The tubulins are in superposition and the collapse of the wave function is driven by the quantum gravity. A string theory model is developed by Nanopoulos (1995) and Nanopoulos & Mavromatos (1996) that is further refined into QED-Cavity model (Mavromatos, 2000; Mavromatos et al., 2002) suggesting dissipationless energy transfer and biological quantum teleportation.

Any physical system is by definition a quantum mechanical system. However, in order for macroscopic quantum phenomena to be observed, it is demanded that the dynamical timescale to be comparable to coherence timescale. Max Tegmark (1999) shows that if the above condition is not met i.e. the coherence time is much shorter than time of dynamics, the system can be well studied by classical physics.

The macroscopic quantum coherence is defined as a quantum state governed by a macroscopic wavefunction, which is shared by multiple particles. *The essence of the* **quantum coherence** *is the existence of nonclassical correlations in the state [entanglement, superpositions].* The quantum coherence typically involves the spaciotemporal organization of the multiparticle system and is closely related to what is

called 'Bose-Einstein condensation'. Examples of quantum coherence in many particle macroscopic systems include superfluidity, superconductivity, and the laser. Of these three paradigm systems, the former two (superfluidity and superconductivity) are basically equilibrium systems, whereas the laser is our first example of an open system, which achieves coherence by energetic pumping - this latter idea is of the greatest importance for understanding the general implications of coherence. The laser functions at room temperature and is typical nonequilibrium possibility for coherence to exist and endure at macroscopic and thermally challenging scales!

According to Georgiev (2003a) the basic neural molecules supposed to organize the intraneuronal space, to receive, process and output information, which sustain macroscopic long-range quantum effects and host consciousness are well known cytoskeletal and scaffold proteins (tubulins, MAPs, actin filaments, CASK, PSD-95, neurexin, neuroligin, protein 4.1 etc.) that constitute the neuronal cytoskeletons and organize the protein communication between the pre- and post-synaptic cytoskeletons.

The coherent transfer of energy along the polypeptide chains, electron density soliton propagation inside the cytoskeletal proteins and long-range quantum entanglement of the neuronal cytoskeletons are supposed to be explanation for how the brain cortex produces and binds the conscious experience!

Georgiev (2003a) claims that the neuronal cytoskeletons are primary residence for consciousness and that the specific protein organization and functions help the quantum mind (macroscopic long-range quantum effects) to control the overall brain dynamics according to the received electromagnetic input. Because the microtubules strongly interact with the local electromagnetic field (QED-cavities!), indeed solitons (local distortions of the electron density) could be generated and could propagate along intraprotein conduction aromatic acid pathways. Mostovoy et al. (1997) study *transpolyacetylene* (a conjugate polymer with single and double bonds), which has a doubly degenerate ground state, and show that the degeneracy allows for topological excitations, solitons, which are kinks in the lattice dimerization accompanied by a local distortion of the electron density. Khaneja & Glaser (2002) note that in the NMR spectroscopy of proteins, the transfer of coherence along spin chains is an essential step in a large number of key experiments. Further they investigate creation of spin encoded states and efficient propagation of these states (via solitons) through the spin chain investigating linear chain of *n* weakly interacting spin 1/2 particles placed in a static external magnetic field in the *z* direction and with Ising type couplings between next neighbours.

It was shown that solitons could affect the protein conformational states and therefore protein dynamics. Caspi & Ben-Jacob (1999, 2002) show that the conformational changes in proteins and the associated protein folding could be induced by the propagation of a solitons along the molecular polypeptide chain, process known as *soliton mediated conformational transition* (SMCT). They conclude that a soliton propagating along a protein backbone provides an effective mechanism for fast and deterministic change in the molecular conformation.

Quantum soliton creation could be induced in microtubules via interaction with the local electromagnetic field. These solitons could be in *superposition* (Gheorghiu-Svirschevski, 2001), when two quantum solitons collide they pass trough each other *getting entangled* and their eventual *collapse* [*dissipation*] after 10-15 picoseconds [time comparable with protein dynamical one] (Georgiev & Papaioanou, 2003) determines the chosen protein states. The ordered water molecule dynamics could shield the *macroscopic quantum entangled state of superposed solitons* up to 10-15 picoseconds in order the cytoskeletal protein network to make use of phenomena characteristic for the quantum world. Because most of the presynaptic proteins are not voltage sensitive they could make use of the information about the electromagnetic field brought by the *microtubular quantum solitons*.
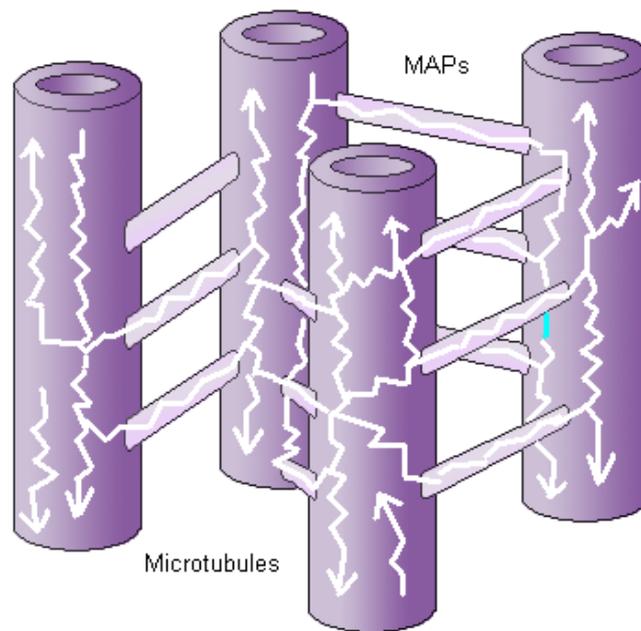

Fig. 1 Microtubules (purple) are interconnected via MAPs and form intraneuronal quantum network. They strongly interact with the local quantized electromagnetic field and generate quantum solitons (white) propagating along conduction pathways formed by aromatic aminoacid residues inside their walls and MAPs.

The propagating *quantum solitons* affect both the cytoskeletal protein conformational transitions and the presynaptic scaffold protein function (thus regulating vesicle tethering, docking and fusion). The presynaptic scaffold proteins causally affect exocytosis via vibrational multidimensional quantum tunnelling and the released neuromediator affects the postsynaptic ion channels.

We can model mind action upon brain via *choosing the output state of the superposed soliton collapse*. Thus mind controls cytoskeletal and scaffold protein dynamics and indirectly postsynaptic membrane potential, while brain *inputs information* to mind directly *using the local electromagnetic field*.

It is expected that observable quantum effects in biological matter be strongly suppressed mainly due to the macroscopic nature of most biological entities, as well as the fact that such systems live at near room temperature. These conditions normally result in a very fast collapse of the pertinent wave functions to one of the allowed classical states. According to Stuart Hameroff (1999) the brain operates at 310K and deviations in brain temperature in either direction are not well tolerated for consciousness. This temperature is quite toasty compared to the extreme cold needed for quantum technological devices which operate near absolute zero. In technology, the extreme cold serves to prevent thermal excitations, which could disrupt the quantum state. However proposals for biological quantum states suggest that biological heat is used to pump coherent excitations. In other words biomolecular systems may have evolved to utilize thermal energy to drive *quantum coherence*. The assumption/prediction by quantum advocates is that biological systems (at least those with crystal lattice structures) have evolved techniques to funnel thermal energy to coherent vibrations conducive to quantum coherence, and/or to insulate quantum states through gelation or plasma phase screens!

2. On the dynamically ordered structure of water

The neural cytoplasm exists in different phases of liquid *sol* (solution), and solid *gel* (gelatinous phases of various sorts, *jello*). Transition between *sol* and *gel* phases depends on actin polymerization. Triggered by changes in calcium ion concentration, *actin* copolymerizes with different types of *actin cross-linking proteins* to form dense meshwork of microfilaments and various types of *gels*, which encompass microtubules and organelles. The particular type of actin cross-linkers determines characteristics of the actin gels. Gels depolymerize back to liquid phase by calcium ions activating *gelsolin* protein, which severs actin (*gel* into *so*l). Actin repolymerizes into gel when calcium ion concentration is reduced (*sol* into *gel*). Actin gel, ordered water phases alternate with phases of liquid, disordered sol. Exchange of calcium ions between actin and microtubules (and microtubule-bound *calmodulin*) can mediate such cycles. The transition between the alternating phases of solution and gelation in cytoplasm depends on the polymerization of actin, and the particular character of the actin gel in turn depends on actin cross-linking. Cycles of actin gelation can be rapid, and in neurons, have been shown to correlate with the release of neurotransmitter vesicles from presynaptic axon terminals. In dendritic spines, whose synaptic efficacy mediates learning, rapid actin gelation and motility mediate synaptic function, and are sensitive to anaesthetics.

Even in the liquid phase, water within cells is not truly liquid and random. Pioneering work by Clegg (1984) showed that water within cells is to a large extent ordered, and plays the role of an active component rather than inert background solvent. Neutron diffraction studies indicate several layers of ordered water on such surfaces, with several additional layers of partially ordered water. Thus the actin meshwork that encompasses the microtubules orders the water molecules in the vicinity shielding the *quantum coherence* between the tubulins!

Jibu et al. (1994, 1996); Jibu & Yasue (1997) describe the dynamically ordered structure of water within the brain. If we denote the spatial region immediately adjacent to the cytoskeletal proteins by V and introduce Cartesian system of coordinates $O_{x,y,z}$ then any point of the region can be labelled by giving its coordinates $r = (x, y, z)$.

This volume is filled with water molecules and ions (the number of ions is relatively small, less than 1% of the total number). Potassium ions (K^+) have radius equal to the radius of the water molecules, so potassium ions can be mixed with water in the dynamically ordered state. Sodium ions (Na^+) and calcium ions (Ca^{2+}) have radii smaller than the radius of the water molecules so they do not disturb the dynamically ordered structure of water. Only chloride ions (Cl^-) do have larger radius than the radius of water molecules. If there are chloride ions in the region, then the system of the radiation field and water molecules will suffer from dynamical disorder and so the dynamically ordered structure of water manifests defects. However the chloride ions have lower concentrations inside the neurons compared to the extraneuronal space.

Further, we fix the total number N of water molecules in the region V. If we look at the jth water molecule (*j* running from 1 to N denotes fictitious number labelling the N water molecules in question), its position will be given by coordinates $r^j = (x^j, y^j, z^j)$. From a physical point of view, a water molecule has a constant electric dipole moment. The average moment of inertia and electric dipole moment of a water molecule are estimated to be $I = 2m_p d^2$ with $d \approx 0.82 \, \overset{o}{A}$ and $\mu = 2e_p P$ with $P \approx 0.2 \, \overset{o}{A}$, respectively. Here, m_p denotes the proton mass and e_p the proton charge. Due to the electric dipole moment μ the water molecule interacts strongly with the radiation field in the spatial region V. Although the water molecules have many energy eigenstates and so can exchange energy with the radiation field in many different values, we restrict the discussion to the case in which only the two principle eigenstates can take part in the energy exchange. These are taken to be low lying states such that either the probability of transition between two other eigenstates is low relative to that between the two principal eigenstates or the equilibrium populations of the other levels become sufficiently small to allow them to be ignored. This coincides with the conventional two-level approximation in describing energy exchange between atoms and the radiation field in laser theory. Then one sees immediately that the quantum dynamics of the jth water molecule can be described by a fictitious spin variable $s^j = \frac{1}{2}\sigma$ in energy spin space, where $\sigma = (\sigma_x, \sigma_y, \sigma_z)$ and the σ_i's are the Pauli spin matrices denoting the three components of the angular momentum for spin ½.

Let ε be the energy difference between the two principal energy eigenstates of the water molecule. Its actual value is $\varepsilon \approx 4\text{meV}$. Then the Hamiltonian governing the quantum dynamics of the jth water molecule is given by εs_z^j and the total Hamiltonian for N water molecules becomes:

$$(1) \qquad H_{WM} = \varepsilon \sum_{j=1}^{N} s_z^j .$$

The two eigenvalues of this Hamiltonian are $-\dfrac{1}{2}\varepsilon$ and $\dfrac{1}{2}\varepsilon$ reflecting the fact that only the two principal energy eigenstates with energy difference ε has been taken into account. Now let's consider the radiation in the spatial region V from the point of view of quantum field theory. It is convenient to describe the radiation field in terms of its effect on an electric field operator $E = E(r,t)$. If it is assumed for simplicity that electric field is linearly polarized, obtaining $E = eE$, where e is a constant vector of unit length pointing in the direction of linear polarization. Then, the radiation field in question comes to be described by a scalar electric field $E = E(r,t)$ governed by the usual Hamiltonian:

$$(2) \qquad H_{EM} = \frac{1}{2} \int_V E^2 d^3 r .$$

Let's introduce the interaction between the radiation field and the totality of water molecules by which they can exchange energy in terms of the creation and annihilation of photons, that is energy quanta, of the radiation field. The electric field operator can be divided into positive and negative frequency parts

$$(3) \qquad E = E^+ + E^- .$$

Then the interaction Hamiltonian of the radiation field and the totality of water molecules becomes

$$(4) \qquad H_I = -\mu \sum_{j=1}^{N} \left[E^-(r^j,t)s_-^j + s_+^j E^+(r^j,t) \right],$$

where

$$(5) \qquad s_\pm^j = s_x^j \pm s_y^j,$$

are ladder operators in energy spin space. The total Hamiltonian governing the quantum dynamics of the radiation field, the electric dipoles of the water molecules, and their interaction is given by

(6) $$H = H_{EM} + H_{WM} + H_I .$$

Since the region V maybe considered as a cavity for the electromagnetic wave, it is convenient to introduce the normal mode expansion of the electric field operator $E = E^+ + E^-$, obtaining

(7) $$E^{\pm}(r,t) = \sum_k E_k^{\pm}(t) e^{\pm i(k \cdot r - \omega_k t)} .$$

Here, ω_κ denotes the proper angular frequency of the normal mode with wave vector k. We are mainly interested in the ordered collective behaviour among the water molecules and the radiation field in the region V, i.e. the vicinity of the cytoskeletal proteins. Let us introduce therefore collective dynamical variables $S_k^{\pm}(t)$ for the quantized electromagnetic field given by

(8) $$S_k^{\pm}(t) \equiv \sum_{j=1}^{N} s_{\pm}^j(t) e^{\pm i(k \cdot r^j - \omega_k t)}$$

and the collective dynamical variable for the water molecules given by

(9) $$S \equiv \sum_{j=1}^{N} s_z^j .$$

Then, the total Hamiltonian becomes

(10) $$H = H_{EM} + \varepsilon S - \mu \sum_k (E_k^- S_k^- + E_k^+ S_k^+) .$$

This total Hamiltonian for the system of N water molecules and the radiation field in the region V around the cytoskeletal proteins is essentially of the same form as Dicke's Hamiltonian for the laser system. Therefore it might be expected that water should manifest laser-like coherent optical activity, that is, act as a water laser.

The coherent behaviour of the water molecules near the neuronal cytoskeletal proteins could shield the macroscopic quantum entangled states of millions neuronal cytoskeletons for 10-15 picoseconds – time comparable with the protein dynamical timescale. Thus when the macroscopic quantum coherent state (wavefunction) collapses faster-than-light enforcement of the output in distant neurons will take place!

3. Synaptogenesis in the mammalian CNS

Information in the brain is transmitted at synapses, which are highly sophisticated contact zones between a sending and a receiving nerve cell. They have a typical asymmetric structure where the sending, presynaptic part is specialized for the secretion of neurotransmitters and other signaling molecules while the receiving, postsynaptic part is composed of complex signal transduction machinery.

In the developing human embryo, cell recognition mechanisms with high resolution generate an ordered network of some 10^{15} synapses, linking about 10^{12} nerve cells. The extraordinary specificity of synaptic connections in the adult brain is generated in five consecutive steps. Initially, immature nerve cells migrate to their final location in the brain (1). There, they form processes, so called axons. Axons grow, often over quite long distances, into the target region that the corresponding nerve cell is supposed to hook up with (2). Once arrived in the target area, an axon selects its target cell from a large number of possible candidates (3). Next, a synapse is formed at the initial site of contact between axon and target cell. For this purpose, specialized proteins are recruited to the synaptic contact zone (4). Newly formed synapses are then stabilized and modulated, depending on their use (5). These processes result in finely tuned networks of nerve cells that mediate all brain functions, ranging from simple movements to complex cognitive or emotional behaviour.

Song et al. (1999) have studied the biochemical characteristics and cellular localization of *neuroligin-1* - a member of a brain-specific family of cell adhesion proteins. They discovered that *neuroligin-1* is specifically localized to synaptic junctions, making it the first known synaptic cell adhesion molecule. Using morphological methods with very high resolution Brose (1999) demonstrated that *neuroligin-1* resides in postsynaptic membranes, its extracellular tail reaching into the cleft that separates postsynaptic nerve cells from the presynaptic axon terminal. Interestingly, the extracellular part of *neuroligin-1* binds to another group of cell adhesion molecules, the *β-neurexins*. Based on their findings, Brose and colleagues suggest a novel molecular model of synapse formation in the brain. Central to this model is the transsynaptic connection between *neuroligins* and *β-neurexins*. This *β-neurexin-neuroligin* junction is formed at the initial site of contact between a presynaptic axon terminal and its target cell. Postsynaptic *neuroligin* interacts with presynaptic *β-neurexin* to form a transsynaptic cell-adhesion complex at a developing synapse. Once the junction is formed, *neuroligins* and *β-neurexins* initiate well-characterized intracellular protein-protein-interaction cascades. These lead to the recruitment of proteins of the transmitter release machinery on the presynaptic side and of signal transduction proteins on the postsynaptic side. The resulting transsynaptic link could also function in *retrograde* and *anterograde signalling* of mature synapses. Once the *β-neurexin-neuroligin-1* junction is formed, a complex cascade of intracellular protein-protein-interactions leads to the recruitment of the necessary pre- and postsynaptic protein components. A functional synapse is formed.

4. The intrasynaptic *β-neurexin–neuroligin-1* adhesion can mediate interneuronal quantum coherence [macroscopic entanglement, superpositions]

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*. Another factor that might contribute to the organization of synapses is the ability of proteins like PSD-95 and CASK to bind transmembrane proteins that mediate cell-cell or cell-matrix adhesion. For example, 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 (Missler & Südhof, 1998). The CASK PDZ domain has also been shown to bind to *syndecans*, which are *cell surface proteoglycans* implicated in extracellular matrix attachment and growth factor signaling (Cohen et al., 1998; Hsueh et al., 1998).

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 (Cohen et al., 1998; Lue et al., 1995). Interestingly, this interaction is mediated by a conserved module in protein 4.1 know as a *FERM domain*, which is known to link other proteins to the plasma membrane (Chishti et al., 1998). 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 (Niethammer et al., 1998). Linkage of these scaffolding proteins to the cytoskeleton might help to stabilize their associated transmembrane proteins within discrete plasma membrane domains.

PDZ-domain-containing proteins create macromolecular signaling complexes at both the pre- and postsynaptic junctions, thus defining the active zone and the postsynaptic density (PSD). Cell-adhesion molecules such as β–neurexin and neuroligin seem to keep CASK and SAP90/PSD-95, respectively, in register at the pre- and postsynaptic plasma membranes. CASK interacts with two PDZ-domain-containing proteins, *Veli* and *Mint1*. The latter binds to the cytoplasmic domain of N-type Ca^{2+} channels. Two novel PDZ-domain-containing components of the presynaptic cytoskeletal matrix are *Piccolo* and *Rim*, which might be involved in mobilization of synaptic vesicles from the reserve to the release-ready pool and in the localization of components of the endo- and exocytotic machinery. At the postsynaptic plasma membrane, PDZ-domain-containing proteins (SAP90/PSD-95; SAP102, SAP97, GRIP/ABP, PICK1) are thought to play a primary role in tethering different glutamate receptors to the postsynaptic cytoskeletal matrix. CRIPT provides a link to microtubules, and another protein called *cortactin* a link to actin. PDZ-domain-containing proteins such as SAP90/PSD-95 and GRIP are also likely to couple glutamate receptors to the Ras signalling cascade. Finally, as is the case at the presynaptic active zone, components of the exocytotic machinery, such as the N-methylmaleimide sensitive factor (NSF), seem to play a role in the trafficking of receptors to the postsynaptic plasma membrane.

We have considered the molecular organization of the synapse to reveal the molecular connection between the two neuronal cytoskeletons and between the presynaptic cytoskeleton and some of the components of the exocytotic machinery. 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 coherence. The entangled cytoskeletons then could act as 'unity' or 'single object'.

5. The β-neurexin-neuroligin-1 adhesions are shielded via ordered water molecules

The intraneuronal proteins can be shielded by the actin meshwork that orders the intraneuronal water molecules, but what about the extracellular β-neurexin-neuroligin-1 link? Can it be shielded against environmental interfering? After all the living cells extract negentropy from their microenvironment so it is supposed that the order inside the cell is overcompensated with chaos outside it. Indeed the extracellular β-neurexin-neuroligin-1 adhesion could mediate interneuronal coherence because it is surrounded by extracellular matrix molecules and could be permanently shielded. Such possible mechanism is shielding by glycosaminoglycans (GAGs), which interconnect the two neural membranes, or polysaccharides and intrasynaptic proteoglycans molecules. Also the chemical synapses are relatively young devices developed in the evolution of the neural system, so they can be considered as insulated compartment via glial muff, whose function is to ensure the interneuronal communication. Thus it can be considered not as extracellular microenvironment, but as specialized intercellular device!
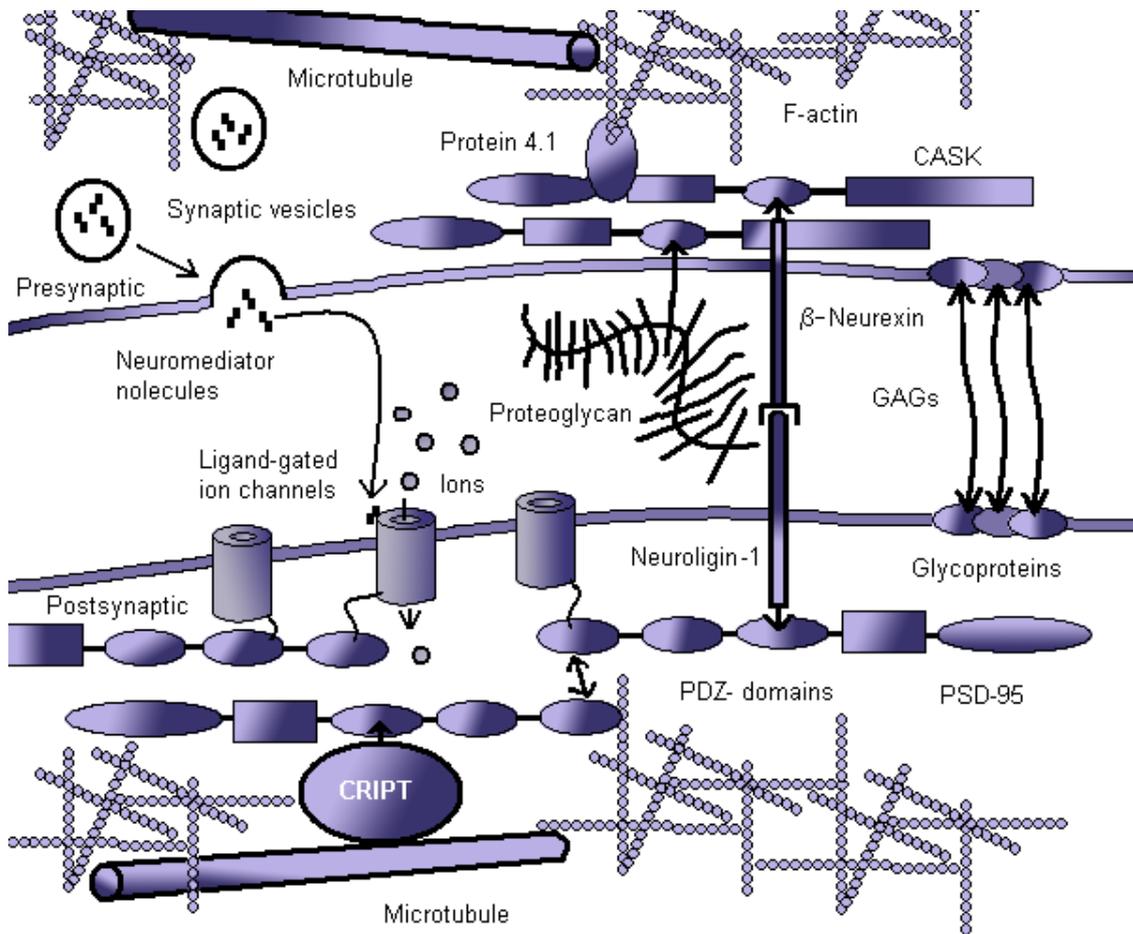
Fig. 2 The β-neurexin-neuroligin-1 adhesion can influence the cytoskeletons of the two neurons. The quantum coherence between neurons is mediated by β-neurexin-neuroligin adhesion which can be shielded by glycosaminoglycans (GAGs) from decoherence.

5.1. Possible shielding mechanism is fucose-galactose bridging of pre- and post-synaptic glycoproteins.

Linda Hsieh-Wilson (2001) has provided experimental data confirming the special role of *fucose* in the brain. Fucose is a simple sugar that is attached to proteins at the synapse and is frequently associated with other sugar molecules. There is some evidence that fucose is important for modulating the transmission of signals between two or more nerve cells. For example, fucose is highly concentrated at the synapse, and repeated nerve-cell firing increases the levels still further. Thus fucose may be involved in learning and memory because disrupting a critical fucose-containing linkage causes amnesia in lab rats. Fucose is often linked to another sugar called *galactose*. The linkage is created when hydroxyl groups on the two sugars combine and expel a water molecule. Rats given *2-deoxygalactose* (which is identical to galactose in all respects except that it lacks the critical hydroxyl group) cannot form this linkage, and develop amnesia because they cannot form the essential fucose-galactose bridging. In another study, rats treated with

2-deoxygalactose were unable to maintain *long-term potentiation* (LTP), which is a widely used model for learning and memory. Taken together, these experiments strongly suggest that fucose-containing molecules at the synapse may play an important role in learning and memory. *Linda Hsieh-Wilson and colleagues* have developed a model that may explain the role of fucose at the synapse. The fucose attached to a protein on the presynaptic membrane can bind to another protein located at the postsynaptic membrane. This stimulates the postsynaptic neuron to make more of the fucose-binding protein, enhancing the cell's sensitivity to fucose and strengthening the connection. In the quantum brain model proposed here the polysaccharides interconnecting the pre and post-synaptic glycoproteins can order the water molecules in the vicinity, so that interneuronal polysaccharide bridges can create ordered microenvironment necessary for β-neurexin-neuroligin-1 adhesion function to entangle the two pre- and post- synaptic cytoskeletons.

5.2. Dystrophin glycoprotein complexes can further provide molecular basis for dynamical water molecule ordering near the β-neurexin-neuroligin-1 adhesions.

Localization studies have determined a neuronal distribution of the dystrophin isoform Dp427, being associated with the postsynaptic density. Three full-length dystrophin isoforms have been established, resulting from different promoters, differing only in their amino-terminal makeup and their cellular location (Culligan & Ohlendieck, 2002). The backbone of the brain *dystrophin-glycoprotein complex* (DGC) is the transmembrane link generated by the presence of α– and β–dystroglycan (Culligan et al., 2001). These proteins act to form an integral plasmalemmal linkage, localizing dystrophin to the subplasmalemmal region. A proline-rich region at the extreme carboxy-terminus of β–dystroglycan mediates this interaction with dystrophin and cross-linking of brain β–dystroglycan results in the stabilization of a high-molecular mass complex (Culligan et al., 1998). The extracellular matrix component α–dystroglycan, a 156 kD heavily glycosylated protein interacts with the amino-terminal region of β–dystroglycan. The polymorphic cell-surface proteins, α- and β-neurexins, have been demonstrated as binding partners for neuronally expressed dystrophin through an interaction with α–dystroglycan. The interaction links the neuronal postsynaptic membrane through α–dystroglycan with the presynaptic membrane through the neurexins, mediating cell aggregation (Sugita et al., 2001). So the neurexin/DGC interneuronal connections can suffice to dynamically order water molecules in the vicinity forming a shield for β–neurexin/neuroligin-1 adhesions.
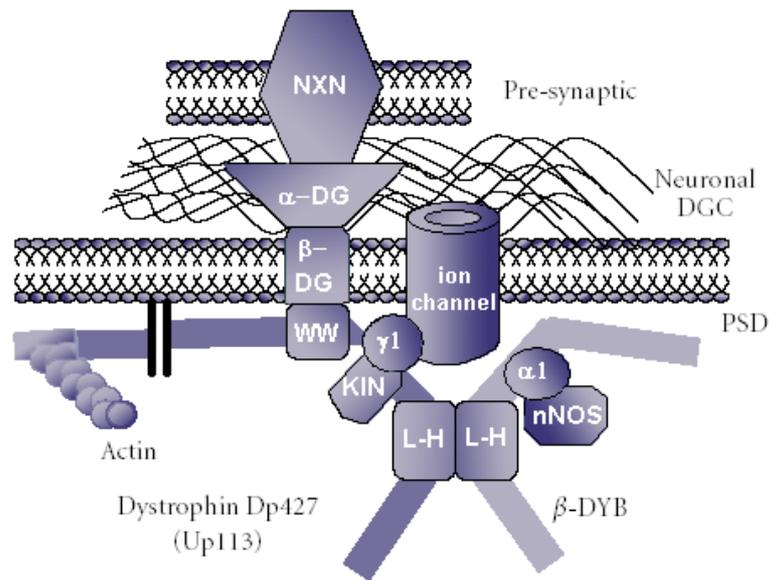
Fig. 3 Schematic representation of the established members of dystrophin-glycoprotein complexes (DGC) and their associations with other peripheral proteins. A dystrophin or utrophin isoforms link to the α/β–dystroglycan (DG) backbone and a dystrobrevin (DYB) isoform. In neurons, α–dystroglycan is associated with neurexin (NXN), linking the presynaptic membrane (PRE) to the postsynaptic density (PSD). Syntrophin isoforms α1 & γ1 recruit neuronal nitric oxide synthase (nNOS) to the complex, as well as other nonestablished voltage-gated ion-channels (Ion Ch) and/or kinases (KIN). Dystrophin domains: WW motif, common to all brain dystrophin isoforms; L-H motif, helical leucine heptads which makeup the coiled-coil domain (picture modified from Culligan & Ohlendieck, 2002)

The role of the dystrophin-glycoprotein complex in synaptic function is further supported by the observation that in one third of the patients affected by Duchenne muscular dystrophy (DMD) there are brain abnormalities, presented in the form of a moderate to severe, nonprogressive mental retardation, are manifest (Mehler, 2000). The abnormality is evident as developmental cognitive and behavioral abnormalities, including deficits in overall and verbal IQ, as well as attention deficits and impaired short-term memory processing (Mehler, 2000; Bresolin et al., 1994).

5.3. Sulfated glycosaminoglycans (GAGs) are linear heteropolysaccharides, which interconnect the pre- and post-synaptic membranes projecting negative charged groups, which can help order the positively charged sodium and potassium ions AND REPELL THE CHLORIDE IONS thus shielding the β–neurexin-neuroligin-1 adhesion.

Glycosaminoglycans (GAGs) like fucose are found at the synapse, are important for proper brain development, and play a critical role in learning and memory (Hsieh-Wilson, 2001). It is believed that, like *fucose*, *glycosaminoglycans* are also involved in establishing connections between nerve cells.

Glycosaminoglycans are complex polymers, having a repeating A-B-A-B-A structure composed of alternating sugar units. There are several different kinds of glycosaminoglycans found in nature, and each GAG is characterized by different sugar units. For example, *chondroitin sulfate* is composed of alternating *D-glucuronic acid* and *N-acetylgalactosamine* units.

In the brain D-glucuronic acid may be chemically modified with sulfate (OSO_3) groups at either or both of the 2- and 3- positions. Every sugar monomer in the glycosaminoglycan molecule is supposed to be slight axially rotated in respect with the previous one. The sulfate groups itself could project in different directions thus contributing a bulk of negative charges in the vicinity ordering water molecules and positive ions. If the GAGs connecting the two neuronal membranes have proper space localization they can permanently insulate the β-neurexin–neuroligin-1 adhesion.

5.4. The neural proteoglycans within the synaptic cleft could also contribute for insulating the β-neurexin–neuroligin-1 pre/post-synaptic adhesion.

The *chondroitin/keratan sulphate proteoglycans* of the nervous tissue may direct the axonal migration. On the other hand, heparan sulphate chains enhance neurite outgrowth, and they also affect the polarity. Extracellular chondroitin sulfate proteoglycans seem to decrease cell-cell and cell-matrix interactions, allowing the cells to round up, divide, differentiate and migrate in the tissue. The ability of heparan sulphates to bind growth factors are possibly important during the growth of differentiation of nervous cells. Except for their crucial involvement in the development of the neural system architecture the proteoglycans stabilize the synaptic structure and fill the synaptic cleft. Here will be paid attention to two neural proteoglycans: *CAT-301* and *phosphacan*.

CAT-301 is a developmentally regulated, high molecular chondroitin sulphate proteoglycan found on the extracellular surface of mammalian neurons. It is expressed late in development and although no definitive role has been identified for CAT-301, it is believed to have a role in the stabilisation of synaptic structure. The name derives from the name of the monoclonal antibody originally used to identify it. Disruption of the normal patterns of neuronal activity during the critical early postnatal period by physical or biochemical means results in a large and irreversible reduction in levels of CAT-301. Similar intervention in mature animals has no effect.

Phosphacan (previously designated *3F8* or *6B4*) is a chondroitin sulphate proteoglycan that binds to neurons and neural cell-adhesion molecules (Maurel et al, 1994; Maeda et al, 1995; Garwood et al, 1999). Cloning of this proteoglycan showed that it has a high homology with receptor-type protein tyrosine phosphatase, formed by alternative splicing (Maurel et al, 1994; Sakurai et al, 1996). It binds with a high affinity to nervous tissue adhesion molecules Ng-CAM and N-CAM, but not laminin, fibronectin, or collagens. Tyrosine phosphatases function together with tyrosine kinases regulating protein phosphorylation, and they can mediate their actions through signal transduction system of the cell.

The consciousness is known to be product of the cerebral cortex activity. We can 'realize' or 'experience' something only if there is proper stimulation of certain areas within the brain cortex. In the β-neurexin–neuroligin-1 quantum model of consciousness the interneuronal entanglement is supposed to occur only between cortical neurons. However arises the question why quantum coherence cannot be achieved between subcortical or spinal neurons considering that β-neurexin–neuroligin-1 link is widely presented in the CNS? I suppose that the answer should come from studying the unique molecular synapse structure between the cortical neurons.

6. The hands of consciousness

If our conscious mind is in the "quantum coherent cytoskeletons" then it should have some power to influence the synaptic activity using its *free will* in a uniform way. This is so because everyone can immediately move his arm, leg etc. or say something. However because nobody can commit to memory at once a poem this means that the conscious thought acts much slower on synaptic plasticity (or other types of memory storage). Such kind of arguments can show us, which brain activities are *immediately* connected with our *free will*, or with the possibility of our mind to collapse the wave function (in milliseconds via fast biomolecular cascades e.g. motion, muscle contraction) and which brain activities are only *influenced* by our "internal thoughts" (slow processes e.g. memory storage, motor protein dynamics and synaptic plasticity etc.). Of course, we are not 'consciously aware' how exactly both types of activities are acted upon by the cytoskeleton – the *mind* action upon *brain* does not include *knowledge* of the very same action i.e. *mind* is not reducible to *knowledge*! Thus 'consciously' our consciousness influences some of the intracellular processes and has diverse effects in the cortical neurons – we cannot say that this action is 'unconscious' just because it has not epistemological component of the mechanism of the action itself [no self-reference paradoxes are relevant here].

Following our own experience we can say that our consciousness has the power to act or not act in specific manner depending on our *free will*. If microtubules just do quantum computing how this could affect the immediate neuromediator release. Nancy Woolf & Stuart Hameroff (2001) suppose that microtubules control the axonal hillock potential but do not provide any concrete mechanism for that. It is quite dubious that such exists, because the axonal hillock potential depends on *voltage gated ion channels (VGICs)* that do open by changes in the membrane potential!

Somehow surprisingly the model including the β-neurexin-neuroligin-1 intrasynaptic adhesions not also answers how interneuronal quantum coherence can be achieved, but also gives answer how the synaptic vesicle release is acted upon. The neurexins are essential ligands for *synaptotagmin* – a protein both acting as a calcium sensor and docking the synaptic vesicle to the presynaptic membrane! The conformational states of β−neurexin can directly or indirectly via *CASK* and *Mint-1* control the exocytosis.
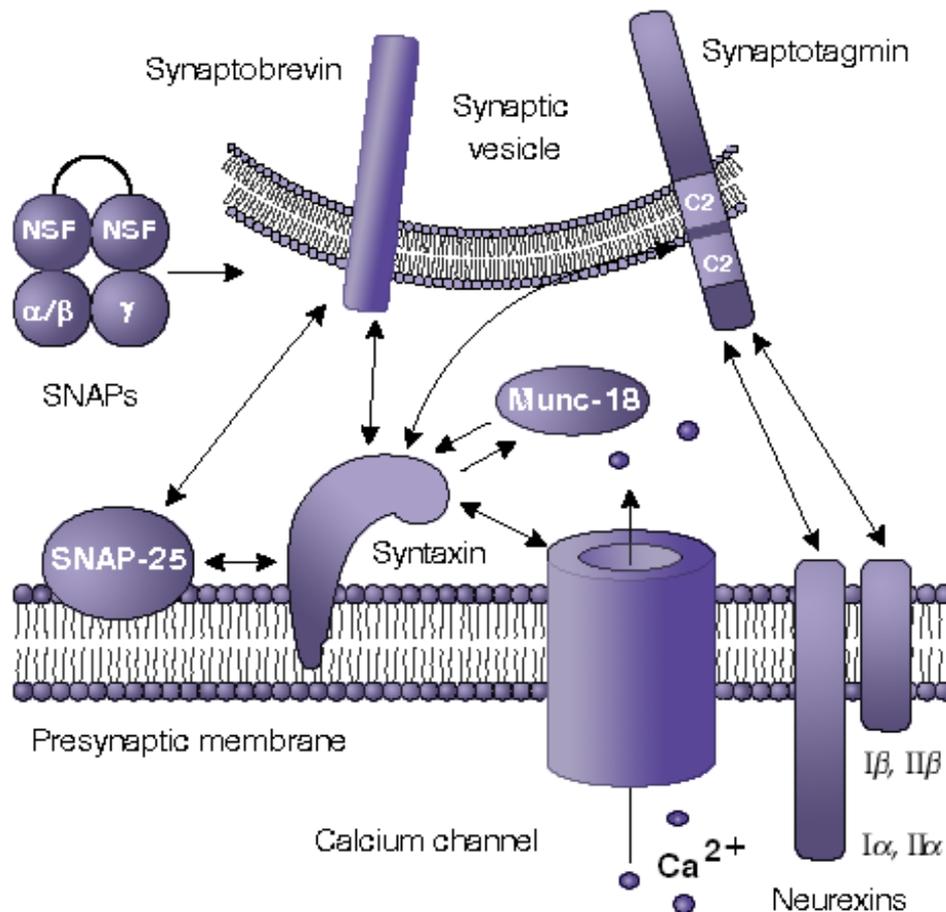
Fig. 4 Exocytotic machinery. The neurexins are major proteins involved in docking the synaptic vesicle to the presynaptic neuronal plasma membrane and facilitating the mediator release. Some other proteins like Munc-18, SNAP-25, synaptotagmin and syntaxin are also taking part in the process.

The basis of the *neuroquantum coherent model of consciousness* is that *mind* is 'fundamental feature' of reality and is something dynamic describable by complex quantum wave born into existence by a conglomerate of entangled proteins – tubulins, MAP-2, neurexin, neuroligin, CASK, CRIPT, PSD-95, actin-binding protein 4.1 etc. In this new model every protein species has its unique intraneuronal function. Thus a fully functional body for the quantum mind is built up!

All intraneuronal processes (synaptic plasticity, memory) are influenced by the 'protein body of the quantum consciousness' – the motor proteins are moving over the microtubules, the β-neurexin-neuroligin link is the core of a new formed synapse, the neuromediator receptors are anchored to and organized by the cytoskeleton, the synapsins are docking the synaptic vesicles to the cytoskeleton, the scaffold proteins drive exocytosis etc. *Thus the neuronal cytoskeletons could be residence for the quantum mind – that is our thoughts, feelings etc.!*
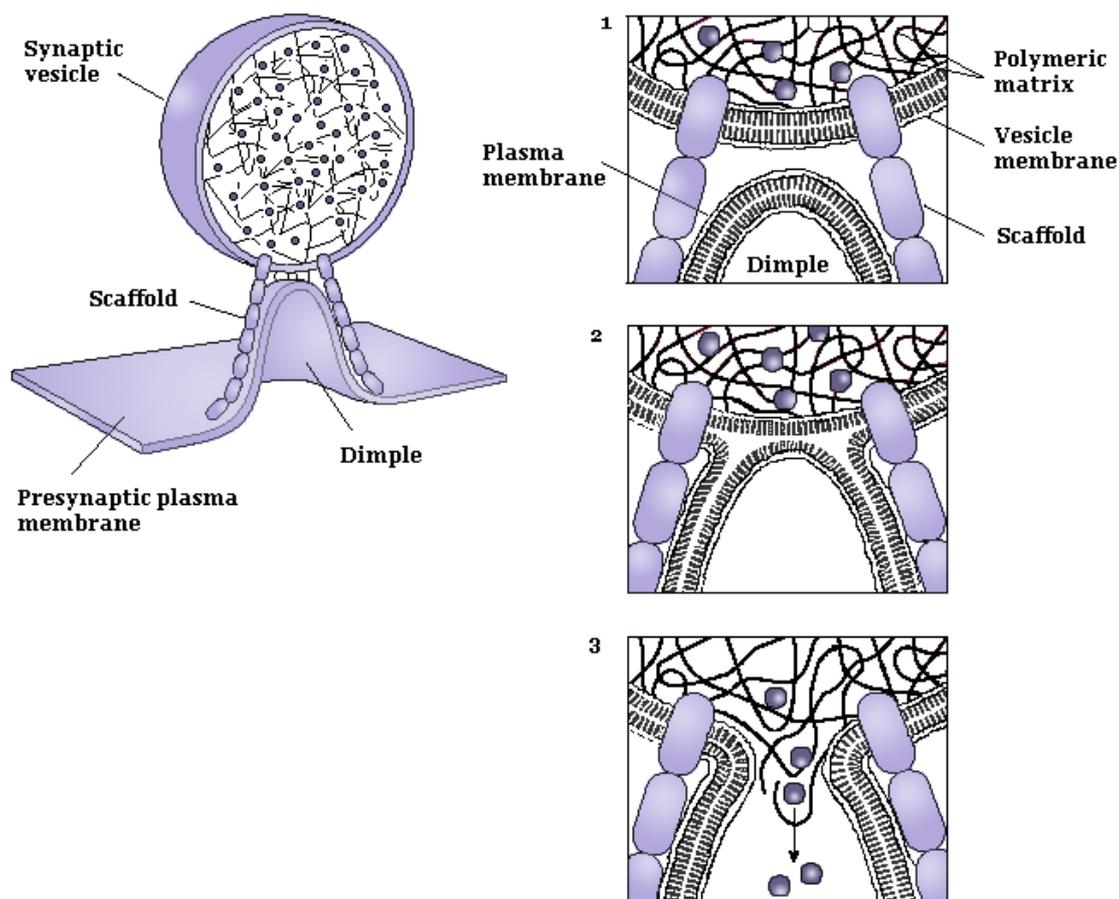
Fig. 5 Diagram of the process of exocytosis by which neurotransmitters in synaptic vesicles at the presynaptic terminal are probabilistically released into the synaptic cleft upon the arrival of an action potential.

Findings by Jack et al. (1981) inevitably imply an activation barrier, which hinders vesicular docking, opening, and releasing of transmitter molecules at the presynaptic membrane upon excitation by an incoming nerve impulse. Redman (1990) demonstrated in single hippocampal pyramidal cells that the process of exocytosis occurs only with probability generally much smaller than one upon each incoming impulse. Deconvolution analysis by Sayer et al. (1989, 1990) has shown that an impulse invading bouton evokes exocytosis (release of neuromediator molecules) with probability 0.2-0.3.

One of the most interesting things about exocytosis is that the synaptic vesicles located in the presynaptic vesicular grid (hexagonal paracrystalline structure) of the axonal bouton manifest long-range correlations (Eccles, 1992; Beck & Eccles, 1992). *There are about 40 synaptic vesicles in the vesicular grid but never does more than one vesicle emit transmitter molecules into the synaptic cleft after stimulation by a nerve impulse!* This certainly means that that the vesicles in the vesicular grid do not act independently but rather that immediately after one vesicle is triggered for releasing its content the interaction between them blocks further exocytosis. The paracrystalline structure of the

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presynaptic vesicular grid makes it possible to have long-range interactions between the constituents, as is well known from ordered quantum systems. Further Beck & Eccles (1992) have calculated that the mass of the quasiparticle that promotes the exocytosis via tunneling is exactly that of a *hydrogen atom*. This supports the idea of *vibrationally assisted tunneling* as trigger for exocytosis as worked out by Georgiev (2002).

Considering the presented data it is safe to assume that only ¼ of the axonal terminals (boutons) release neuromediator under firing. This will produce complex geometric pattern of active (~25%) and silent (~75%) boutons that surely must be controlled by the conscious experience. The fact that a single axon forms synapses with dendrites from hundreds of other neurons ["labeling" each synapse; making synapses distinguishable] and the relatively small number of released vesicles makes the idea of their random (chaotic) release untenable.

In the synaptic vesicle release there are involved great number of proteins (SNAPs, synaptotagmin, synaptobrevin, β−neurexin, syntaxin) and because there is an energy barrier their function can be compared with the enzyme catalytic action. According to Stuart Hameroff (1998) the London quantum forces set the pattern for protein dynamics. A year later Basran et al. (1999) suppose vibration driven extreme tunneling for enzymatic H-transfer. At the beginning of 21st century the Haldane's notion of 'imperfect key' about the biological catalysis in classical over-the-barrier manner is questioned. Sutcliffe & Scrutton (2000a) underline that matter is usually treated as a particle. However it can also be treated as a wave (wave-particle duality). These wavelike properties, which move our conceptual framework into the realm of quantum mechanics, enable matter to pass through regions that would be inaccessible if it were as a particle. In the quantum world, the pathway from reactants to products might not need to pass over the barrier but pass through the barrier by quantum tunnelling. Quantum tunnelling is more pronounced for light particles (e.g. electrons), because the wavelength of a particle is inversely proportional to the square root of the mass of the particle. Electrons can be tunnelled for distance of about 2,5 – 3 nm. Protium can tunnel over a distance of 0,058 nm with the same probability as an electron tunnelling over 2,5 nm. The isotopes of hydrogen – deuterium and tritium have increased mass and tunnel with the same probability over 0,041 nm and 0,034 nm. *Klinmann and co-workers* were the first to obtain experimental evidence consistent with H-tunnelling in an enzyme-catalyzed reaction on the basis of deviation in kinetic isotope effect from that expected for classical behaviour. Since their proposal of H-tunnelling at physiological temperatures in yeast alcohol dehydrogenase (Cha et al., 1989), they have also demonstrated similar effects in bovine serum amine oxidase (Gant & Klinman, 1989), monoamine oxidase (Johnsson et al., 1994) and glucose oxidase (Kohen et al., 1997). Tunnelling in these systems was described in terms of static barrier depictions.

The pure quantum tunnelling reactions are temperature independent, because thermal activation of the substrate is not required to ascend the potential energy surface. However the rate of C-H and C-D cleavage by methylamine dehydrogenase was found to be strongly dependent on temperature, indicating that thermal activation or '*breathing*' of the protein molecule is required for catalysis. Moreover, the temperature dependence of

the reaction is independent of isotope, reinforcing the idea that protein (and not substrate) dynamics drive the reaction and that tunnelling is from the ground state. Good evidence is now available for *vibrationally assisted tunnelling* (Bruno & Bialek, 1992; Basran et al., 1999) from studies of the effects of pressure on deuterium isotope effects in yeast alcohol dehydrogenase (Northrop & Cho, 2000). Combining the experimental evidence, the argument for *vibrationally assisted tunnelling* in biological catalysis is now compelling! The dynamic fluctuations in the protein molecule are likely to compress transiently the width of the potential energy barrier and equalize the vibrational energy levels on the reactant and product site of the barrier (Sutcliffe & Scrutton, 2000b; Scrutton et al., 1999; Kohen & Klinman, 1999). Compression of the barrier reduces the tunnelling distance (thus increasing the probability of the transfer), and equalization of vibrational energy states is a prerequisite for tunnelling to proceed. Following transfer to the product side of the barrier, relaxation from the geometry required for tunnelling "traps" the H-nucleus by preventing quantum 'leakage' to the reactant side of the barrier.

Catalysis is driven by quantum fluctuations that affect the protein conformations. We could therefore generalize that every protein driven process (transport, muscle contraction, exocytosis) could be referred to as a catalysed process and thus quantum in nature. The most important here is to note that the pure quantum tunnelling is temperature independent. In contrast most of the proteins have evolved mechanisms to utilize the thermal energy – *vibrationally assisted tunnelling.*

7. What is vibrationally assisted quantum tunnelling?

There are principally two ways by which an energy barrier can be surpassed in the existing biological processes: the classical over-the-barrier thermal activation and quantum through-the-barrier tunnelling. Usually it is thought that the characteristic difference between the two mechanisms is the strong temperature dependence of the former, while the latter is independent of temperature, and only depends on the energies and barrier characteristics involved! However, only pure quantum tunnelling is temperature independent. If the tunnelling is multidimensional there could be both classical degrees of motion and tunnelling in phase space, and the process could be promoted or suppressed by the thermal fluctuations (mixed quantum tunnelling).

7.1. Thermal activation. This leads, according to Arrhenius' law, to a transfer rate, *k*, of

$$(11) \qquad k \sim V_C \exp\left(-\frac{E_A}{k_b T}\right),$$

where V_C stands for the coupling across the barrier, and E_A denotes the activation barrier.

7.2. Quantum tunnelling. There exist two types of tunnelling: one-dimensional and multi-dimensional. The quantum tunnelling could also be *pure tunnelling* when the particle has only quantum motion inside the energy barrier (temperature independent) and mixed tunnelling when the particle has both quantum plus classical possibility for its movement.

7.2.1. Pure quantum tunnelling. In this case the transfer rate, *k*, is determined by

$$(12) \qquad k \approx \omega_0 \exp\left(-2\int_a^b \frac{\sqrt{2M[V(q)-E]}}{\hbar} dq \right)$$

where *V(q)* is the potential barrier; *a* and *b* denote the classical turning points for the motion left and right of the barrier, *E* is the energy of the particle undergoing tunnelling, and ω_o is the number of attempts that the particle undertakes to reach the barrier (Beck & Eccles, 1992).
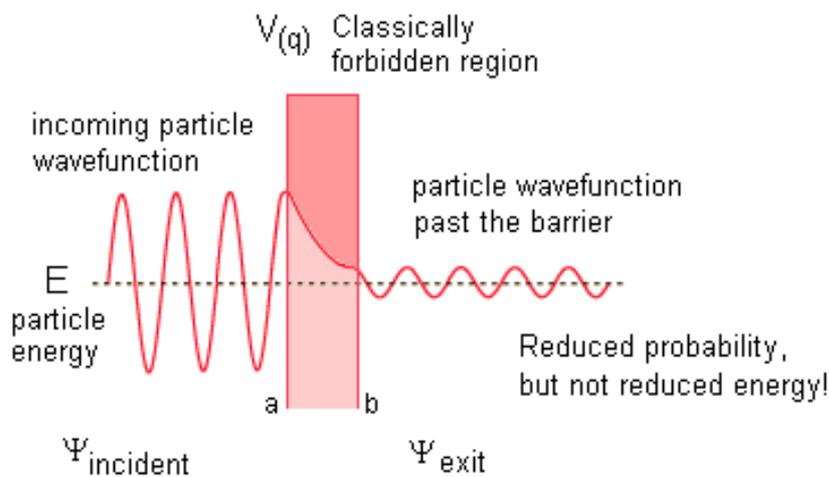

Fig. 6 Schematic representation of the tunnelling process. According to classical physics, a particle of energy E less than the height $V_{(q)}$ of a barrier could not penetrate - the region inside the barrier is classically forbidden. But the wavefunction associated with a free particle must be continuous at the barrier and will show an exponential decay inside the barrier. The wavefunction must also be continuous on the far side of the barrier, so there is a finite probability that the particle will tunnel through the barrier.

7.2.2. Mixed tunnelling. One of the most outstanding differences between one-dimensional and multidimensional tunnelling is the existence of mixed tunnelling in the multidimensional case. The mixed tunnelling is such a tunnelling that classical motion is allowed in one or more directions in the multidimensional space. In contrast in the pure tunnelling classical motion is not allowed in any direction. The *vibrationally assisted tunnelling* is a kind of *mixed tunnelling*.

It was found that there are three kinds of vibrational modes with respect to the effects of the excitation on tunnelling; 1) those which do not affect the tunnelling, 2) those which promote the tunnelling, and 3) those which suppress the tunnelling. If there is no coupling between the tunnelling coordinate and the co-ordinate transversal to it, the vibrational excitation in the latter does not affect energy splitting. This corresponds to the first type. When there is a coupling between the two coordinates, it is natural to expect from the

analogy with the one-dimensional case that the vibrational excitations promote the tunnelling. However, the experimental findings in *tropolone* molecules clearly show that the real proton tunnelling is not so simple. This fact nicely exemplifies the complexity of multidimensional tunnelling.

Takada & Nakamura (1995) show that depending on the topography of potential energy surface (PES) vibrational excitation either promote or suppress the tunnelling and that the mixed tunnelling plays an essential role in suppression and oscillation of energy splitting against vibrational excitation. The general Wentzel–Kramers–Brillouin (WKB) theory of multi-dimensional tunnelling developed by Takada & Nakamura (1994) provides us with a clear conceptual understanding of the multidimensionality. The theory was formulated by solving the following basic problems: 1) construction of the semiclassical eigenfunction in classically allowed region according to the Maslov theory, 2) its connection to the wave function in the classically inaccessible region, and 3) propagation of the latter into the deep tunnelling region.

It became clear that there exist two distinct tunnelling regions: C-region where action is complex and I-region where action is pure imaginary. Tunnelling in these regions is qualitatively quite different from each other; in the I-region the tunnelling path can be defined by a certain classical trajectory on the inverted potential, while in the C-region there is no unique path and the Huygens type wave propagation should be applied.
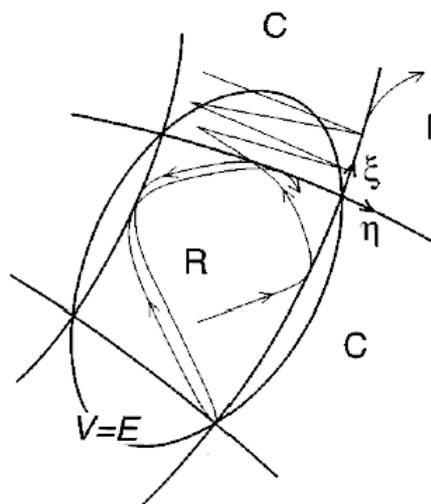

Fig. 7 Schematic drawing of the physical picture of tunneling obtained by the WKB theory. The classical trajectories comprising a quantum eigenstate are confined within the distorted rectangular region (called R-region), although the much wider region is energetically allowed (see the oval region bounded by V=E. The tunnelling proceeds first to the C-region where the motion in ξ-direction is non-classical (tunnelling), while the motion in η-direction is still classical. Takada & Nakamura (1995) call this type of tunnelling 'mixed tunnelling.' At the boundary between the C-region and I-region, part of the tunnelling wave enters into the I-region where no classical motion is allowed in any direction. This conventional type of tunnelling is called 'pure tunneling'.

Table 1. Characteristics of multidimensional tunnelling obtained by the WKB theory. The table summarizes the characteristics of the tunnelling in each region. It should be noted that the wave function in the C-region has nodal lines, but that in the I-region does not. This plays an important role in the effects of vibrational excitation on tunnelling.

Region	Characteristics
R-region	Classically allowed Nodal pattern
C-region	Mixed tunnelling Tunnelling in ξ-direction Classical in η-direction No tunnelling path Nodal lines
I-region	Pure tunnelling No classical motion Tunnelling path Classical trajectory on $-V(x)$ No nodal line

Takada & Nakamura (1995) have investigated the effects of vibrational excitation on tunnelling using several model systems: tunnelling energy splitting of excited states have been obtained by the exact quantum mechanical calculation and have been interpreted by the WKB theory and the sudden and adiabatic approximations. Various interesting effects have been found: 1) In the case of the *symmetric mode coupling* (SMC) model, vibrational excitation always promotes tunnelling. 2) In the case of *antisymmetric mode coupling* (ASMC), pure tunnelling in I-region is promoted by the excitation, while mixed tunnelling in C-region is either promoted or suppressed. The latter is attributed to the phase cancellation in the overlap integral of Herring's formula. 3) In the case of squeezed potential, vibrational excitation suppresses the tunnelling when the squeezing effect is sufficiently weak, while strong squeezing makes the tunnelling irregular.

8. Retrograde signalling during learning-dependent changes in synaptic connectivity

Both, neuroligins and β-neurexins are the cores of well-characterized intracellular protein-protein-interaction cascades. These link neuroligins to components of the postsynaptic signal transduction machinery and β-neurexins to the presynaptic transmitter secretion apparatus. It provides an interesting and simple mechanism for retrograde signalling during learning-dependent changes in synaptic connectivity. Indeed, the β-neurexin-neuroligin-1 junction allows for direct signalling between the postsynaptic nerve cell and the presynaptic transmitter secretion machinery. *Neurophysiologists and cognitive neurobiologists have postulated such retrograde signalling as a functional prerequisite for learning processes in the brain!*
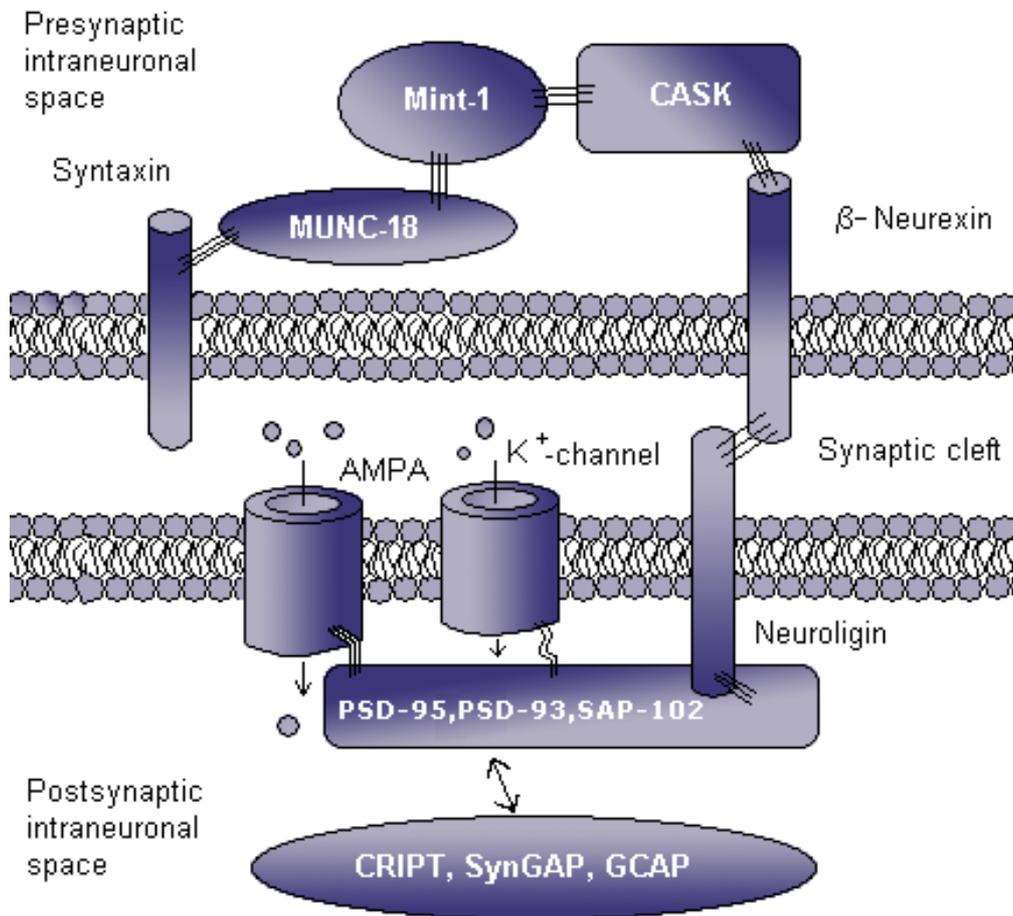
Fig. 8 The β-neurexin-neuroligin-1 junction transmits retrograde and anterograde biological information between the pre- and post-synaptic cytoskeletons (via quantum solitons?). CASK and Mint 1 are presynaptic PDZ-domain proteins with a scaffold function; Munc18 and syntaxin are essential components of the presynaptic transmitter release machinery; PSD95, PSD93, SAP102, and S-SCAM are postsynaptic PDZ-domain proteins with a scaffold and assembly function that recruit ion channels (e.g. K^+-channels), neurotransmitter receptors (e.g. NMDA receptors) and other signal transduction proteins (GKAP, SynGAP, CRIPT).

9. Cellular adhesive molecules (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.

10. 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.
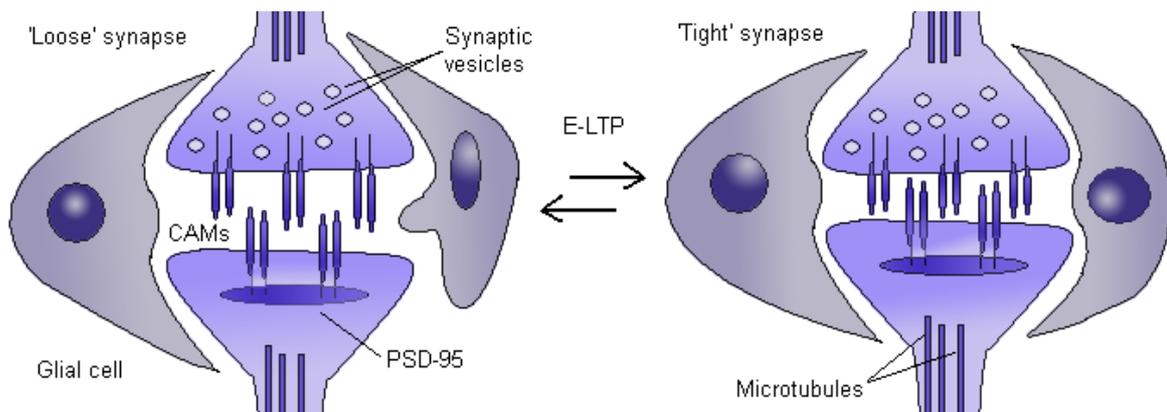

Fig. 9 Early-long term potentiation (E-LTP) after tetanizing stimulation.

11. How could activity-induced changes in adhesive strength affect synaptic physiology?

11.1. 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).

11.2. Quantum possibility in the brain cortex:

Altering the distance between the two neural membranes may act as switch for the β-neurexin-neuroligin-1 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 (Georgiev, 2003b).

12. 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 remodeling.
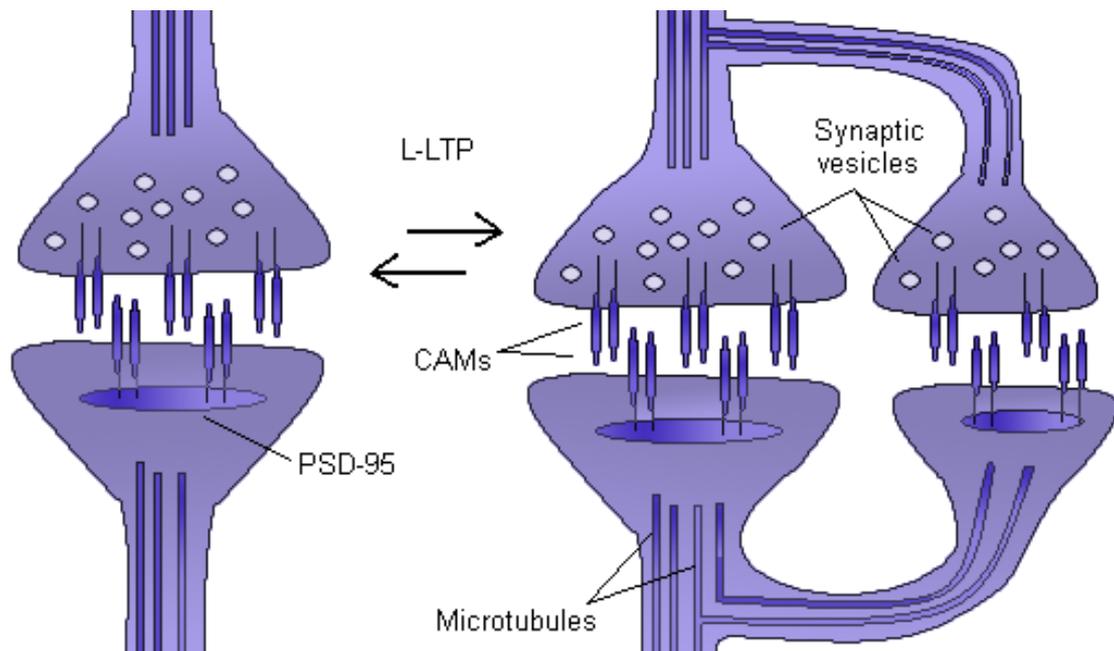
Fig. 10 Long-term plasticity (L-LTP). The presynaptic neuron extends axonal projections and forms new synapses.

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.
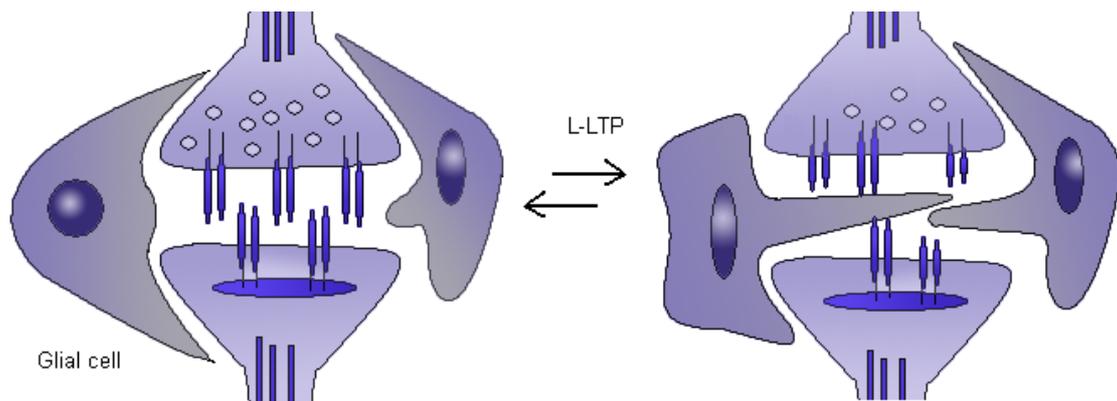

Fig. 11 Long-term synaptic plasticity: reversible glial cell barrier at active synapses.

13. 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.

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.

14. 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). 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-1 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-1 switch!

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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