"Computational Neuropsychiatry" of Working Memory Disorders in Schizophrenia: The Network Connectivity in Prefrontal Cortex – Data and Models

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Abstract

The use of mathematical and computer-assisted modeling of brain mechanisms involved in mental disorders can be called "Computational Neuropsychiatry". It was already demonstrated by several initiatives that computational modeling is an important contribution to understand neuronal circuits that could generate mental functions and dysfunctions. However, this attempt needs close collaboration between experimental neurobiologists, clinical psychiatry and systems science. In order to do so, we have organized a series of workshops on computational neuropsychiatry. Here we try to give basic information on data and modeling of the prefrontal cortical neurocircuitry that is involved in working memory and its disorders in schizophrenia. Special emphasis is devoted to the basic features of computational modeling.

"Computational (Systems) Neuropsychiatry" – towards a theoretical systemic neuropsychiatry

Biological psychiatry has gathered an increasing amount of data that throws some light on the brain mechanisms of mental disorders like schizophrenia. Now, the problem arises to put together the various pieces of knowledge into a coherent picture of the functions and dysfunctions of the brain. One difficulty at the attempt to understand normal and pathological brain functions is the complexity of data. Another problem is related to the conceptual integration of the variety of methods that are used to investigate the brain such as imaging techniques, animal experiments, histological preparations, electrophysiology, molecular biology, genetic tools and other techniques. All these methods generate a heterogeneous picture of the neurobiological correlate of various behavioral processes. Finally, the complexity of the brain itself as a hypercomplex network with estimated trillions of neuronal connections makes it impossible to understand it's functions and dysfunctions and dynamics of processes by imagination alone.

In experimental neurobiology already methods from the theoretical sciences like mathematics, systems science, cybernetics, informatics, computational sciences and theoretical physics are used to build models in order to understand the network properties of the brain. This new field often is called "Computational Neuroscience" [5, 19]. Saying it briefly, Computational Neuroscience studies neuronal computation with the help of computer-assisted mathematical tools [19, 33, 20]. To give an example: one of the most famous theoretical approach is the model of the electrical reactivity of the neuron as it was proposed by Hodgkin and Huxley [35;comp.37]. Their model could describe the dynamics of the exchange of ions between the extracellular and the intracellular space thus generating the membrane potential and spikes of a single neuron. This concept in neural modeling is represented mostly in integrate-fire models as they were constructed by Fitzhugh and Nugamo [comp. 37]. This nonlinear model of the neuron is the basis of most other "naturalistic" spiking models that are constructed to describe and explore the behavior of more complex neural networks in the brain [4, 5].

Regarding this theoretical approach of computational neuroscience also pathological information processing in the brain could be considered within a mathematical framework that could be called "Computational Neuropsychiatry" [70]. For instance, the known neurochemical circuits involved in generating schizophrenic symptoms can be studied by computer-assisted analyses

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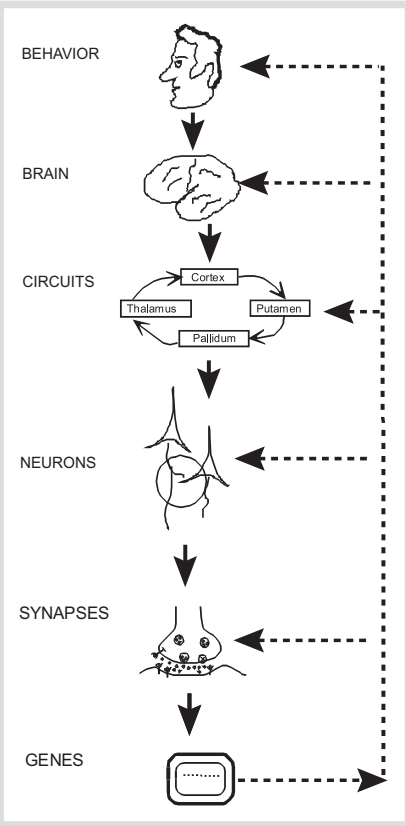

Fig. 1 The reductionistic approach – top-down process of empirical and experimental neuroscience und the problem to reconstruct the whole and to explain bottom-up macro-phenomena by micro-phenomena [modif. from 7].

and simulations [7,68,69]. Lately, in molecular biology and genetics a new systemic approach is emerging, called "Systems Biology" that is devoted to computerized reconstruction of the functions of the cells (e.g. growth, differentiation, apoptosis) on the basis of molecular signaling, metabolic and gene regulatory networks [1,40,41,52]. Not yet, systems biology is established in psychiatry [69]. For this reason it might be reasonable to call systemic neuropsychiatry as "Computational Systems Neuropsychiatry" because Computational Science and Systems Biology have to be brought together in order to proceed in the field of theoretical neuropsychiatry.

With the aim to initiate this systemic way of thinking in biological psychiatry we have started with a series of workshops devoted to the integration of clinical psychiatry, experimental neurobiology and computational sciences. Our First International Workshop on Computational Neuropsychiatry was organized in fall 2005 with support by Arvid Carlsson. At that workshop we discussed theoretical models that were centered around the neurobiological circuitry concepts developed by Arvid Carlsson [14,58,68,70]. We also decided then to concentrate in our 2006 workshop on the analysis and modeling of the prefrontal cortex (PFC) regarding working memory functions. We focussed on the dopamine signaling system in the PFC.

The following questions were addressed and discussed in this workshop and are represented in this volume: What is the neurobiological basis of working memory and its disturbances [s. Winterer (p. S45), Gallinat et al. (p. S40), Schlösser et al. (p. S85), Haenschel et al. (p. S54) in this issue]? How are working memory functions generated in neural networks [s. Loh et al. (p. S78), Haenschel et al. (p. S54), Schlösser et al. (p. S85) in this issue]? What does dopamine really "do" in the cortex [s. Leuner and Müller (p. S17), Winterer (p. S45), Meisenzahl (p. S62), DiPietro and Seamans (p. S27), Gallinat et al. (p. S40) in this issue]? What are the differential effects of antipsychotics [s. Leuner and Müller (p. S17), Koch (p. S34) in this issue]? What kind of models help us to understand these processes in local networks [Vogels and Abbott (p. S73), Loh et al. (p. S78) in this issue]? Here, in this paper we give an overview of our current theory-oriented discussion.

Basic issues of systemic modeling – integrated multi-level perspective

Systems science (or systems research) – based on mathematics, physics, electrical engineering, theoretical chemistry and similar disciplines – is the pool of interdisciplinary applications of systems thinking and systems modeling. This field still only sparsely is established at universities and colleges. Systems science understands the subject under study to be an entity being composed of several interdepending parts being organized on different levels such as cells and cellular networks [comp. 7]; (**Fig. 1**). Several concepts as stability, non-equilibrium, dynamic equilibrium, modularity, feedback, deterministic chaos, non-linearity, robustness etc. characterize this field of theorizing [7,66,68].

Systems science has provided several methods that allow to formulate models of the processes being studied. One main feature of this modeling methodology is the formulation of a wiring diagram that represents the conceptualization of the interactions between the various components of the system. Additionally, systems research has provided a pool of mathematical methods such as differential equations, Petri nets, Markov chains etc. that allow to model the system. This formalization is the basis for the computerization of the model that is necessary in order to make virtual experiments (simulations of scenarios). Many components of the tools of this methodology were derived from the "world models" developed by Jay Forrester and are now mainly represented in management science by what is known as the "System Dynamics" approach [63]. Details concerning modeling and the systemic approach were published within the context of our 2005 workshop [7, 68;see also 82].

Systemic modeling takes account of the fact that the subject to be modeled is a complex network composed of a large number of units (nodes) that show a large number of connections (edges). These are crucial properties of the brain and this is the reason to relate to systems science as a theoretical science. Modern physics and chemistry has shown that elementary particles, atoms and molecules but even simple systems like pendula can exert nonlinear behaviour that can hardly be predicted. This phenomenon is known as chaotic behaviour (chaos theory; 53]. Also extreme large systems make it hard to understand processes, a fact that is known as the complexity problem (complexity theory; 8, 45]. Therefore, the study of non-linear dynamics and complexity can be related to the field of systems science.

Some authors cover the same area of studies but call it "Computational Science" or "Informatics". When applied to (neuro) biological research various prefixes are used like "Computational Neuroscience", "Bioinformatics" or "Neuroinformatics" [5].

Structure of models – "atomic" modules of networks

The main problem in modeling is the decision to select the significant features of the real system and to represent only an appropriate subset of components and relations of the real sys-

tem in the model in order to generate the targeted function of the network that should be explored. Most systems researchers use the "artificial neural networks" approach. This approach involves mapping the real system consisting of millions of components in a matrix of hundreds or even thousands of interconnected units, where the connections activate or inhibit the target units in the network and where the flow of signals runs forwards and backwards etc. [for details, see 4,5]. Also these networks consist of a basic pattern of connectivity that can be reduced to basically structured functional modules. In principle, a group of "atomic" elementary functional two-component modules can be identified that either consist of (I) two activators (ACT-ACT) or (II) of one activator (ACT) and one inhibitor (INH) or (III) of two inhibitors (INH-INH; **Fig. 2**). Depending on the kinetic coupling properties, they tend to exhibit escalatory (I), oscillatory (II) or polarizing behavior (III).

Usually the global balance of activation and inhibition is important for the function of the network [s. Vogels & Abbott, this volume].

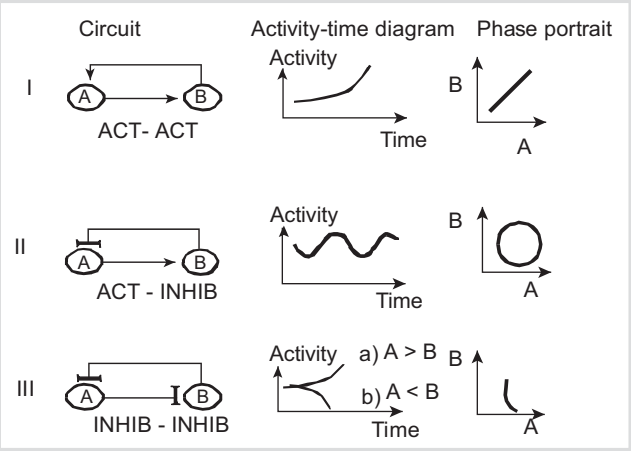

Fig. 2 Elementary two-component modules consisting of activators and inhibitors with different activity patterns and phase portraits [modif. from 67].

Many systems researchers, like Jay Forrester, argue that "atoms" and "molecules" that represent the functional modules that comprise complex systems should be sought (**Fig. 3**). Also in biochemical systems theory (Systems Biology) some authors try to find canonical circuits in molecular networks that they call "motifs" [1]. The concept of "canonical modules" seems to be important for our discussion, as several concepts of modular units are proposed by several authors with regard to the cortex – the "columns" being one example (s. below).

Such basic "atomic" modules can be found as components in more complex networks (**Fig. 3**). They show the following principles of connectivity:

- (local) self-activation/-inhibition
- lateral activation/inhibition of parallel pathways (or modules)
- multi-stage feedback activation/inhibition
- multi-stage feedforward activation/inhibition
- multi-input module (convergence)
- multi-output module (divergence)

For instance, in the CNS such modules can be identified in the multi-layer neuronal network of the retina (reciprocal lateral inhibition) and in the spinal cord (antagonistic/synergistic inhibition). The (oscillatory) central pattern generator, as an activator-inhibitor module [34], also exhibits a functional structure that can be derived from such elementary modules. These basic modules can be seen in every brain circuit, whereby each element of these modules can represent a population of even thousands of neurons. The same is true for intracellular biochemical networks [40]. For a qualitative (or: semiquantitative) understanding of these circuits, the actions can be analyzed in relation to one another by mathematical methods or by exploratory numerical simulations [58].

It should be kept in mind: Selection from the complexity of "reality" is the basis of modeling, but selection implies the risk of neglecting essentials - doing the right thing could be the art of modeling.

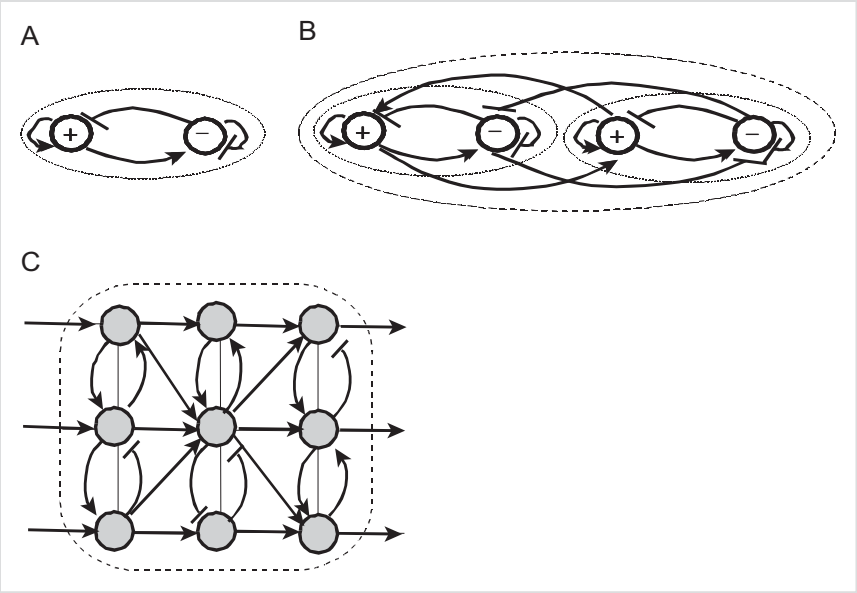

Fig. 3 (**A**) "Atomic" two-component module, with mutually interacting activator (+) and inhibitor (−) and with self-activation and self-inhibition. (**B**) "Molecular" module, consisting of two atomic modules, with mutual ("lateral") activation and mutual ("lateral") inhibition. This module corresponds to the "canonical circuit" of Shepherd [59], which will be described below. The behavior of the atomic module was described before, the activity of the molecular module can not be understood by imagination alone, only computer simulations can help. (**C**): Multi-layer network with 9 nodes and 3 inputs and 3 outputs and 22 unidirectional connections. The behavior of the network and its' components has to be explored by a computer-based model.

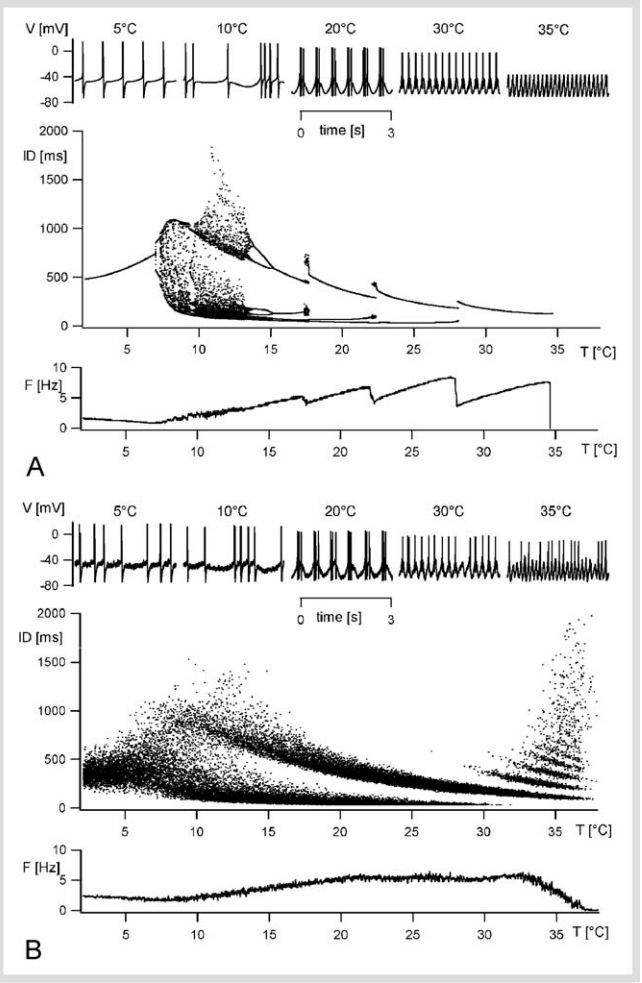

Fig. 4 Spike patterns, bifurcations and mean spike-frequencies of cold fibers depending on temperature. The problem of choosing the appropriate measure of neuronal activity (upper trace in **A** and **B**): interval between discharges (ID) or frequencies of temperature dependent discharge patterns [**F**]. Bifurcation diagram when modelling with (**A**) deterministic approach and with (**B**) approach with noise. More valid simulation by using noise: irregular pattern at high temperature occurs as observed in nature (lower right). ordinate: discharge voltage (mV), interval of discharges (ID), frequency (Hz), abscissa: temperature; [repr. with perm. from 9].

Modeling the activity of networks and their components – levels of data resolution

When trying to model processes in the nervous system, one of the first questions is related to the decision what kind of signals should be used for modeling in order to represent the behaviorally significant activity of the brain. In computational neuroscience, most authors use biophysically based models that reflect ion currents in the models of single neurons and in networks [19]. This modeling strategy represents membrane potentials and action potentials ("spiking models", **Fig. 4**). Such cellular models allow to study the discharge activity of each neuron even in the context of a complex network model under various conditions. The respective networks, accordingly, consist of several hundred neurons that exert excitation and inhibition. However, for exploratory modeling purposes of networks spiking frequencies of a train of spikes can be transformed by a sliding time window into a continuous curve [19].

One further problem that arises is connected with the conceptualization of the variability in these actions – are the discharges random patterns or chaotic patterns, what is the functional significance of bursts etc.? It is well known that experimentally recorded discharge activity of sensory systems (e.g. cold fiber action potentials) can exert regular low-frequency discharges, brief bursting discharge patterns or high-frequency discharges [9], (**Fig. 4**). For understanding this neural code, a measure must be found, that represents the variety of the discharge patterns of (a) a single nerve cell and (b) of a population of neurons. Simple frequency measures, for instance in the form of Hertz as action potentials per second, is not sufficient since it does not represent the variation of patterns. Therefore, interspike intervals are often calculated and represented as histograms. Hans Braun [9] represented a method that is based on mathematics of nolinear processes (simply saying: "Chaos theory"). A visual representation of this computation is possible by bifurcation diagrams that represent the characteristics of the discharge patterns very clearly. This can be seen, for example, by several frequency bands of discharges of some nerve fibre that are observable for one specific temperature (**Fig. 4A**).

A further problem now also exists when trying to include the generators of the spikes in a formal approach, as spikes originate during "upwards fluctuations" of the membrane potential (upstate). It is assumed that these fluctuations essentially are caused by the local signals arriving onto the cell, mainly caused by excitatory postsynaptic potentials (EPSP's) of glutamate or acetylcholine transmission and/or inhibitory postsynaptic potentials (IPSP's) induced by GABA inputs. Therefore, the phenomenon of switching from membrane fluctuations into the all-or-nothing - signals of the spikes formally is represented in Integrate-and-Fire-Neuron models. The irregular pattern of these postsynaptic potentials (PSP's) can then be represented in a formal model by random signals with small amplitudes that express excitatory and inhibitory signals. Because of the thousands of synapses and the (not only there) available receptors that generate the PSP's modeling becomes too vast and is also formally too unhandy. Therefore, a sinusoidal oscillation and/or a sine-wave can be used formally in order to represent processes that exert an on-off pattern with maxima and minima. This function can also be transformed generally into a differential equation of undamped oscillation: the second derivative of position as a function of time (acceleration) represents this curve very well. If in a next step a delta function is introduced that depends on a threshold (e.gf. – 20 mV) then the model shows various discharge patterns that correspond to physiological spike patterns. Furthermore, the fluctuations of the baseline can be superimposed by random variations (noise). This formalization allows to simulate a discharge pattern that appears very "naturalistic" (**Fig. 4B**).

Finally, the activity of a population of cells has to be described in a proper way. When modeling a population of neurons the discharges can be represented with the same strategies as described before. Another possible way is to refer to the electrical local field potential (LFP) that reflects the activity of several neurons in the vicinity of the recording micropipette. Intense deviations of LFP correspond to synchrony of firing of neurons that is an important parameter for cognitive processes as Singer and his group were showing [61, 62;see also Haenschel et al. in this volume]. Therefore measures of coherence are important variables for modeling of proper functioning of neural networks: Oscillations of neuronal networks with a frequency of about 30–70 Hz seem to be important for cognition. This experimentally proven

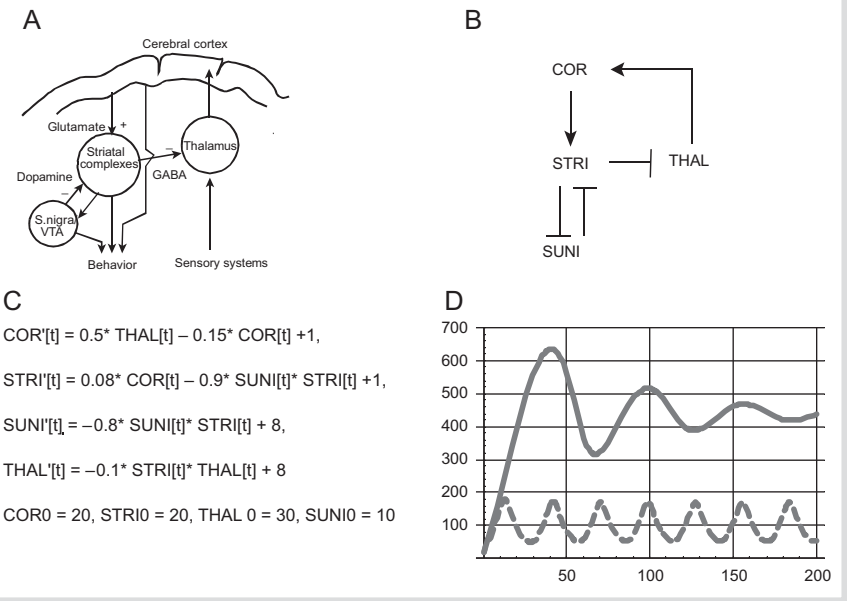

Fig. 5 Steps of mathematical modeling – from anatomy to simulation. **A**: Anatomically defined neuronal circuits [after 11]. **B**: Schematic of circuit. **C**: Differential equations and estimated parameters. **D**: Regular oscillatory behavior in simulated normal case (dotted line) and damped oscillation with a higher cortical level of activation (solid line) at simulated schizophrenia by overactivation of the dopamine signal transmission system (abscissa: arbitrary units of time, ordinate: arbitrary units of activity level). Comments: COR = cortex, THAL = Thalamus, SUNI = Substantia nigra, STRI = Striatum.

phenomenon can also be reproduced in an artificial neural network model of working memory functions [76,77].

Regardless of these sophisticated and naturalistic techniques of modeling neuronal activities, for first-step qualitative exploratory studies more simple measures can be used: For preliminary understanding of the qualitative dynamics of a network indicators with arbitrary units and that are normalized to scales ranging from 0 to 100 can be used. Also the time scale often is represented by arbitrary units. Such models allow to study the qualitative properties of the dynamics of the respective network. Only in a next step of modeling a more precise quantification takes place. Regarding this fuzzy strategy to build models, it must be kept in mind that models never should represent the total reality – therefore, not every detail must be included in the model.

Systems modeling of neurobiology of schizophrenic symptoms

We must first state clearly that, in spite of a number of simplifications that we will have to make later on, schizophrenia is seen as a disease with an extremely complex symptomatology. Furthermore, from a diagnostic point of view, several forms of schizophrenia are distinguished within the framework of the ICD. In this paper, we will focus on the impairment of cognitive functions such as working memory [81]. At present the most emphasized theory of schizophrenia is based on a neurodevelopmental concept that assumes that dysfunctions of genetic factors determine a dysfunctional connectivity mainly of the dopaminergic system [46; s. also Winterer (p. S45) in this issue]. Still such qualitative models are not yet transformed into computational models that allow to demonstrate the functional consequences of the assumed morphological disturbances. However, several attempts already were made to build computational models that simulate symptoms of schizophrenia [e.g. 15, 36].

The basic model by Carlsson

Here we try to demonstrate the test of a qualitative systemic model of neuronal circuitry of schizophrenia that is related to the basic heuristic model designed by Carlsson in 1988 [11]. In this model, Carlsson emphasized the relevance of dopamine in macroanatomical circuits within the context of glutamate and GABA, where he explained the hypothetical occurrence of information overflow in the cortex by hyperactive dopamine transmission in the striatal complexes (◉ **Fig. 5**). The global neurochemical circuitry of this model has to be translated into a wiring diagram to make the functional structure of the network explicit. A set of differential/difference equations has to be constructed and "exploratory" computer simulations may be performed in addition [68]. From a systemic point of view, the principle of this circuit is based on the effects of a serial double inhibition (disinhibition) that origins in substantia nigra and that results in a hyperactivation of the target structure (here: the thalamus). As circuits imply "circular causality" also low glutamate input into the striatal complexes and/or low GABA output of these nuclei could evoke a hyperactivation of primary sensory cortices that receive thalamic input. This is in line with various other neurochemical hypotheses of the development of productive symptoms in schizophrenia [12,13]. Only the role of serotonin is ignored in this basic model but is was integrated in the last complex model by Carlsson [14]. From a systemic multilevel perspective, this model can also be extended as the circuitry of the "striatal complexes" including the substantia nigra has many subsystems. This was also shown by Carlsson in his lecture in our workshop in 2005 [14], where he also emphasized the fact that circular causality and the convergence of activation and inhibition must be taken into very careful consideration. For exploratory reasons it is possible and useful to reduce the complexity of the model and therefore it serves only as a demonstration of basic modeling procedures.

The computerized exploratory model

A typical modeling procedure starts with the qualitative anatomically and neurochemically defined model that represents the mode of connectivity in a qualitative way by indicating acti-

Table 1 State of the prefrontal neural network depending on the functional dominance of the respective dopamine receptor subtype – State 1 is D2R-dominated, state 2 is D1R-dominated [modif. from 80]

Dominant receptor	D2R	D1R
State of network	State 1	State 2
Receptor action	Firing ↓ GABA-AR ↓ NMDAR ↓	Firing ↑ GABA-AR↑ NMDAR ↑, AMPAR ↓
Input state of network	"Gate" open	"Gate" closed
Effects	Easy access to working memory buffers. Multiple network representations	Initiation and stabilization of a few goal-related representations
Dysfunctions	Any internally or externally derived representation can guide action. Result: random, tangential or intrusive thoughts or actions	Only the strongest representations affect action, but they do so completely. Result: narrowing of stimuli selected for action leading to stereotyped or obsessive thoughts or actions.
Implications for schizophrenia	Positive symptoms are already treated by D2R receptors antagonists but D1/D5R agonists might have added benefit by biasing the system towards State 2	Targeted blockade of D1R receptors in PFC might alliviate negative symptoms related to narrowing of thoughts and attention

Comment: GABA-AR = Gamma-amino-buteric-acid receptors, NMDAR = N-methyl-D- aspartate receptors, AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxacolepropionic acid receptors

vating and inhibiting connections (● **Fig. 5A**). This neurobiological model is transformed into a wiring diagram (● **Fig. 5B**) that represents the functional structure and that in a next step allows to formulate difference equations or differential equations (● **Fig. 5C**). These equations represent virtual level variables indicating the average discharge activity of the neuronal population in the respective brain structure. The change of the intensity of these variables is also based on assumptions that are not yet tested experimentally. It must kept in mind, that at present, for theoretical neuropsychiatry we do not have the appropriate measurements of these variables and their kinetics. In spite of this, the widely applied methodology of systemic modeling uses "dummy variables and data" in order to study the characteristics of the dynamics of the system. The values of these dummy variables are estimated by numerical computer simulations. By several tests the behavior of the system under normal conditions and under pathological conditions (● **Fig. 5D**) is described and discussed. The normal condition shows cortical oscillations, the pathological situation shows a higher level of activation and a damped oscillation, indicating a tendency to persist in a high level of mental activity. As a next step the structure of the model and the selection of the significant variables must be improved. The properties of this model can also be discussed by formal analysis [58].

Working memory - the prefrontal cortex function

As the dopamine-based transmission system is the neurochemical "common denominator" of all antipsychotic drugs, the effects of dopamine on cognitive functions are of interest, as dopamine is theoretically assumed to have state-dependent tuning effects (filter functions, "gating functions") on the prefrontal cortical network [25]. Additionally, it is a well based finding that patients with schizophrenia have a dysfunction of the dopamine system and an impairment in working memory functions. Experiments give evidence that subjects with hypofunction in working memory performance have an impairment of dopamine transmission in the prefrontal cortex [81]. They can improve by amphetamine application [54]. However, amphetamine can reduce working memory function in subjects that have a normal dopamine function (● **Fig. 6**). Experiments show that high dopamine input into

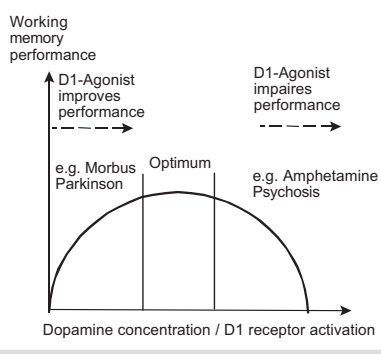

Fig. 6 Empirical inverted u-function representing the relationship between dopamine level and working memory performance. Both, excessive and insufficient D1 receptor stimulation reduce performance [modif. from 54].

the PFC diminishes cognitive functions in the same way as a reduction in dopamine [29, 30, 31]. The pharmacological determination of dopamine agonists shows that the activation of D1 receptors (D1R) seems to be crucial: Regarding this finding, several authors have focused on the ratio of D1 receptors versus D2 receptors (D2R, ● **Table 1**); [25, 54, 55, 72]: if the network is dominated by D1R a strong working memory function can be performed. If D2R dominate, a weak working memory function is performed, however the patient shows a high ability to associate. Therefore, with regard to the D1R-mediated signaling system, it is assumed that optimal dopamine input is a "medium level" of concentration of this transmitter (● **Fig. 6**; ● **Table 1**) [24, 54, 55, 77, 75; see alsoWinterer in this volume]. In consequence, low dopamine concentrations might result in focussed and persistent dopamine D1R–dominated activation of the PFC network with only a few nodes of activation (gate closed, state 2). In contrast, high dopamine concentrations probably lead to an activation pattern of the network characterized by a dopamine D2R-dominated defocused state with multiple activated nodes (gate open, state 1). This state may be related to working memory deficits (perseveration and instability because of "hyperflexibility" in thinking) in schizophrenia [77].

A high ratio of cortically present (and/or activated) D1R vs. D2R and an "optimal" level of dopamine release are supposed to be crucial for sufficient signal-to-noise ratio to provide undisturbed information processing (state 2). In this state of the network, a few representations are present, and in extreme cases this could correspond to obsessive thoughts or action. Consequently, in

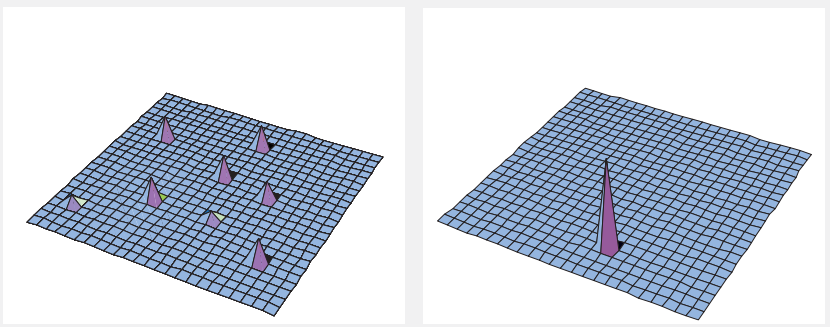

Fig. 7 Theoretical prefrontal neuronal network states with regard to processing mnemonic information: D2 receptor-dominated state with multiple, but weak transient centers of activation and D1 receptor-dominated state with singular but strong and sustaining center of activation [25, 54, 77, s. also Winterer in this volume]; (graph generated with Mathematica®).

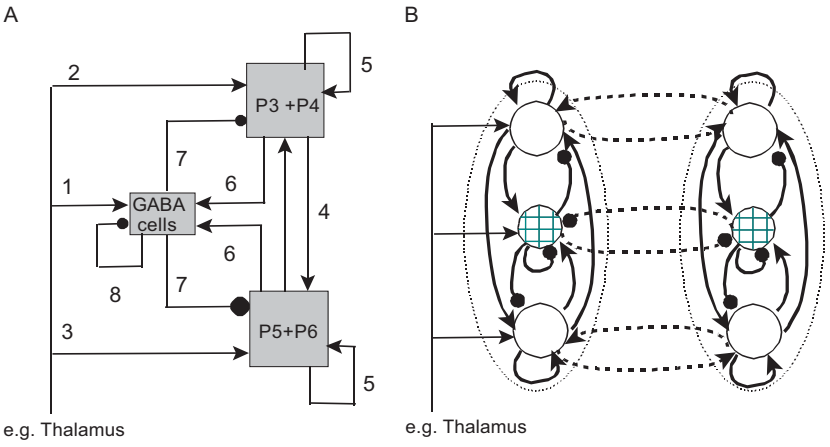

Fig. 8 Diagram of a "canonical circuit" [59] in cerebral cortex (**A**), and hypothetical diagram of circuitry with two coupled canonical circuits (**B**). 1,2,3 = subcortical inputs (here: also dopaminergic inputs), 4 = reciprocal activation, 5 = recurrent activation, 6 = activation, 7 = inhibition, 8 = recurrent inhibition.

state 2 pharmacotherapeutical D1R blockade could help to reestablish a functional equilibrium again.

On contrary, a D2R-dominated state of the network (state 1) might allow a low threshold access to memory buffers, so that any representation in the network can guide the action. This results on the clinical level in the incoherence of thought and action (**Fig. 7**). Therapeutically, additional activation of the D1R channel could help. According to this view, fluctuating levels of dopamine activity in the PFC could lead to dysfunctional switching between high and low tuning states [s. also 14, 24, 78]. Additionally, the dominance of the D2R- vs. the D1R-based dopamine signaling channels in PFC must be seen in context of a diminished glutamate and GABA transmission (**Table 1**).

It should be also considered that during working memory performances additional areas are involved. This is also relevant as in patients with schizophrenic symptoms a significant difference of topographical cerebral activation pattern compared to healthy subjects is observed [56]. This aspect indicates that this PFC network model probably represents only a to simple perspective.

Structure of the (prefrontal) cortical neuronal networks

Looking to a histological slice of the cortex one sees a tremendous complexity of cells and connections with about 50,000 cells in each mm^3 and about 6,000 synapses on each neuron, which means that this small network has about $3 * 10^8$ connections [59, p.7]. The structure of cortical areas is similar all over the cerebral cortex. Furthermore, the microscopically visible vertical connections support the concept that cortical columns, on general, are relevant elementary modules for cortical processing (**Fig. 8**). This was postulated by the studies of Janos Szentagothai [64] and, in the visual cortex, in particular, by David Hubel and Torsten Wiesel [38] and in the motor cortex by Vernon Mountcastle [47].

As far as frequency and size are concerned, the pyramidal cells are the dominant cell type within neuronal circuits of the cerebral cortex ("canonical neurons"), [59]. These cells have vertically and horizontally distributing outputs via glutamatergic fiber connections to themselves, to other pyramidal cells, to several inhibitory interneurons and to other intra- and extracortical structures. In spite of this complexity, some researchers think that the most elementary module of a cortical network consists of an excitatory pyramidal cell and an inhibitory cell with extracortical inputs for each cell [59]. Although this circuit is simple (**Fig. 3**) the behavior may be very complex: A model for such a

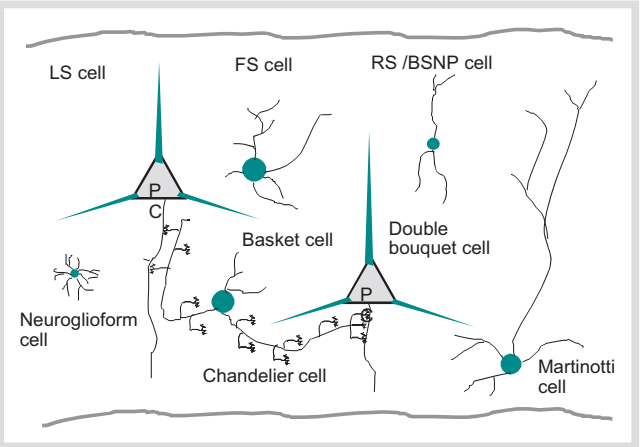

Fig. 9 Scheme of several types of inhibitory neurons in the cortex: Chandelier cell, Basket cell, Double Bouquet cell, Martinotti cell [simplified from 39]. LS = late-spiking neurons, FS = fast-spiking n., BS = burst-spiking n., RS = regular-spiking n, BSNP cells = non-pyramidal cell (NP) with burst-spiking (BS) activity.

circuit was presented by an der Heiden in our 2005 workshop, based on former work with Glass and Mackey [2]: The simulation shows under various mathematical and biophysical assumptions that the recurrent inhibition (self-inhibition) of pyramidal cells can generate a rather irregular pattern, depending on the number of GABA receptors. This pattern is similar to that generated by simulations by Braun (s. above). Therefore it can be speculated, that variation of strength of inhibitory feedback is crucial for shaping the neuronal signaling on the level of ion channels as well as in neural networks.

In this context, it is assumed that subcortical projections into the cortex – at least in sensory areas – converge on stellate cells or small pyramidal cells, which converge with their axons on layer 3 and layer 4 pyramidal cells. Thus, in the primary visual area, stellate cells or small pyramidal cells, as "simple cells", are assumed to be the first input stage, showing simple receptive fields (light-on/-off sensitive areas separated), whereas pyramidal cells in a later input stage (e.g layer V) have the receptive field properties of "complex cells" (light-on/-off sensitive areas mixed). Cell assemblies coding the same field in the visual space and the same orientation of elongated visual stimuli are assumed to represent a cortical column. The output of pyramidal cells projects convergently on hierarchically "higher" cortical areas (e.g. temporal cortex), theoretically ending up with "master neurons" that should be able to recognize one's grandmother (also: "cardinal neurons", acc. to Horace Barlow [6]). Some authors assume that this organization principle is represented in all cortical regions. The intracortical connectivity with regard to self-recurrent excitatory connections between pyramidal cells was already detected by Lorente de No [44] and has been used in the concepts of artificial neural networks. This circuitry could be responsible for retaining information and it could be modulated by inhibitory neurons

The significance of inhibitory cortical neural networks

It must be mentioned here that the differential role of inhibitory neurons has only been taken into consideration recently. Much information is now available on the structure and functions of inhibitory neurons in the (prefrontal) cortex. The most important

Table 2 Terminology for inhibitory cortical neurons according to axon targets, immunohistological properties, electrophysiological properties and morphological features [39]

perisoma-targeting cells (PTC)	dendrite targeting cells (DTC)	interneuron targeting cells (ITC)
parvalbumin-containing c. (PV)	calbindin-containing c. (CB)	calretinin-containing c. (CR)
fast-spiking (FS) cells	spike-frequency adaptation	irregular spiking patterns (often: bursting pattern),
large Basket cell type and Chandelier cells.	cells with narrow dendritic and axonal arbors	narrow dendritic and axonal arbors

inhibitory neurons mainly release GABA. Several types of neurons can be identified, however, this typology depends on the methodology by which the cells were determined: electrophysiologically, anatomically or histochemically etc. [17,18,21,39,72,73]; (**Fig. 9**; **Table 2**).

- Widespread inhibition is mediated by perisoma-targeting cells (PTC), which are parvalbumin-containing (PV) and fast-spiking (FS) neurons. They project to pyramidal cells. Morphologically they are large Basket-cells type and Chandelier cells.
- Within a cortical column, calbindin-containing (CB) interneurons with narrow dendritic and axonal arbors target the dendrites of pyramidal cells (DTC). CB cells show spike-frequency adaptation.
- Locally connecting calretinin-containing (CR) interneurons, also with narrow dendritic and axonal arbors, preferentially project to CB cells (= interneuron targeting cells, ITC) and thus functionally speaking mediate disinhibition. Electrophysiologically CR neurons cells are characterized by irregular spiking patterns (often: bursting pattern), [21].

Douglas et al. [23] are of the opinion that the structure-function relationships of inhibitory cortical neurons are not yet clear. As will be shown later, the circuitry of inhibitory neurons may play a crucial role in networks performing working memory functions [72,74,75]. This is interesting as deficiencies of inhibitory neurons are also relevant for schizophrenia [43].

The (prefrontal) local cortical network and dopamine

The basic neuronal structure of PFC networks has been investigated by the experimental neurobiologist Patricia Goldman-Rakic [e. g. 30]. The findings of her working group and also the observations of Charles Yang have been used for computerized network models by Wang [77], Durstewitz [24] and Deco [22].

Neocortical pyramidal cells receive direct glutamatergic thalamic projections as well as dopaminergic, serotonergic, norepinephrenergic and cholinergic projections from the brain stem and also from other subcortical structures [60]. Additionally, taking into account that two classes of pyramidal cells (PC) and one class of inhibitory neurons (IN) characterize the basic structure of the cortical neural network, the role of dopamine can be considered then [41,50,51] (**Fig. 10**): Pyramidal cells (PC) have glutamatergic outputs and also receive input by synapses based on N-methyl-D- aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxacolepropionic acid (AMPA) recep-

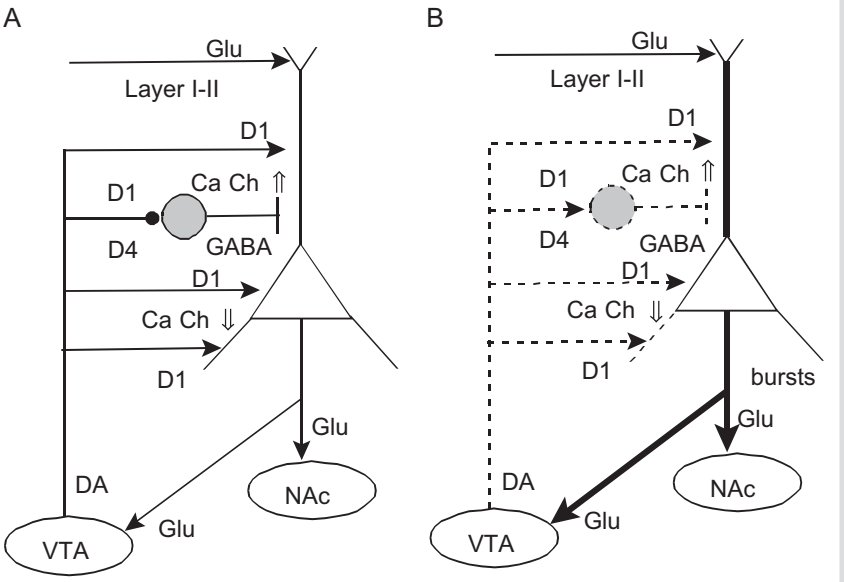

Fig. 10 Summary of a dopamine-based microcircuit theory of functional disorders in PFC in schizophrenia [modified from 54]. **A**: Normal activation of pyramidal cells (PC) when dopamine input is normal. **B**: Weak dopamine input enhances activation of PC if D1R dominate inhibitory neurons. Thus high reactivity of the PC occurs with regard to inputs onto apical dendrite in layer I and II. This corresponds to high distractibility by other intracortical inputs. ⊣ = inhibition, → = excitation, —● = modulation, depending on concentration.

tors. NMDA receptors are weak and slow in exciting the respective cell, whereas AMPA receptors are very effective in evoking postsynaptic currents, thus evoking responses with a brief latency. NMDA receptors seem to be predominant at recurrent synapses. Inhibitory neurons (IN) mainly use GABA as a transmitter substance. Dopamine input is received by receptors of the D1R family and of the D2R family on PC and IN. It is still not determined if PC are controlled more by D1R- or by D2R-based transmission. This is also unclear with IN [50]. In this model, based on findings of the working group of Goldman-Rakic [30] D2R are supposed to be expressed by inhibitory neurons, whereas the working group of Yang suggests that D1R are predominantly present in inhibitory neurons [55, 74]. Also electrophysiology is not conclusive as Gao and collaborators [28] by activation of D1R found a reduction of inhibitory effects of fast spiking inhibitory interneurons that target soma of pyramidal cells, whereas Seamans and his group [e.g. 54] found this effect to be mediated by D2R. One explanation is the dependence of D1R on the level of the membrane potential [24]. This issue remains unresolved mainly as electrophysiological recording of inhibitory neurons is not easy [50].

Regarding such connectivity, Yang and collaborators [72–74] proposed a cortical cellular input-output model for schizophrenia that will be briefly described here (**Fig. 10**). The basic module is composed of a pyramidal cell (PC) receiving inhibitory input by a GABA-ergic FS inhibitory neuron (IN). Both cells receive dopamine input from ventral tegmental area (VTA), the PC via D1R and the IN via D1R and D4R. The PC projects to VTA and to Nucleus accumbens (NAc). Several conditions can be distinguished with regard to working memory (**Fig. 10**):

- Normal dopamine input in PFC activates D1R on pyramidal cells and D1R and D4R on inhibitory neurons. The result would be a medium level of activation of pyramidal cells.
- Hypoactivity of dopamine would result in weaker D1R-based activation of FS interneurons that would lead to weaker inhibition of apical dendrites and could thus lead to bursts and other abnormal discharge patterns.
- Hyperactivity of dopamine would result in strong activation of D1R. This might lead to an increase in the self-activation and co-activation of local pyramidal neurons (not depicted here).

This model should be extended because the intracortical canonical circuits should be integrated detailed in this view. Also the subcortical connectivity should be regarded in order to represent the relevant systems that are connected with PFC networks. This model already shows that computational modelling might be difficult at this stage as many connections are not yet determined sufficiently (**Fig. 11**).

In this view the dopamine system acts as a modulator that shapes cortical activity patterns. In schizophrenia dopamine seems to play a central role not only with regard to the occurrence of productive symptoms by overactivity of mesolimbic transmission but also based on a hypofunction of dopaminergic transmission in prefronatal cortex being correlated to impaired working memory function [s. Leuner and Müller (p. S17) in this issue]. However, dopamine also is important for reward and addiction. It is supposed that midbrain dopamine centers are involved in signaling of "reward prediction error" [57]. The functional role of dopamine in the brain must therefore be re-examined in more detail [54, 57]. The monkey experiments of Wolfram Schultz in recent years led to a completely new differentiated viewpoint of the function of the dopamine system [57]. Out of the four subsystems of the brain's dopamine system, the system that projects from the midbrain to nucleus accumbens is identified as the reward system. This system exhibits phasic and tonic activity: phasic activity is coding rewards, whereas tonic activity represents the baseline, absence of an expected reward evokes phasic inhibition of activity. The discovery that the dopamine system signals the "reward-prediction-error" means the following [57]:

- During unexpected rewards, on the basis of spontaneous activity a strong but short (phasic) activation of the neurons occurs.
- If an expected reward occurs no modification of the discharge is observed.
- If an expected reward does not occur, a reduction of activity of that neuron takes place.

In this view, the global behavioral function of the dopamine system appears to act as an "optimizer" of the current brain state

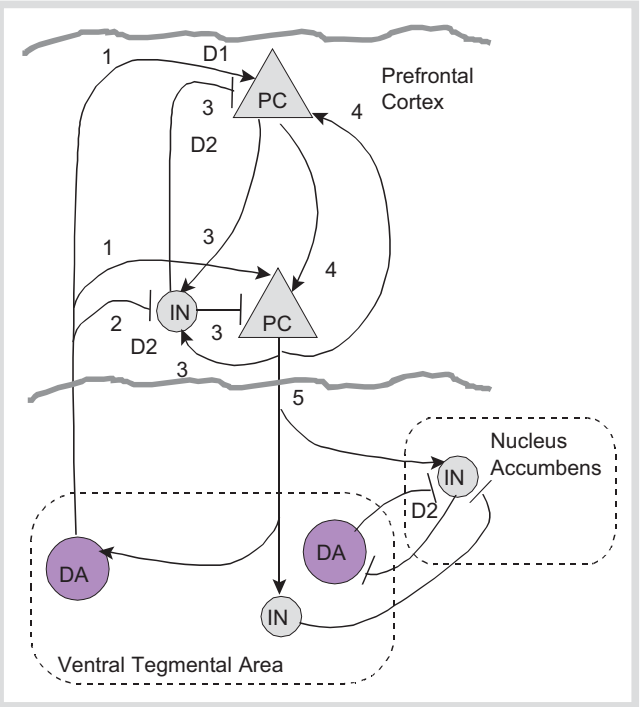

Fig. 11 Neurobiologically based diagram of the modular "canonical" prefrontal cortical micro-circuit and connections with the dopamine system (modified from 30, 59, 72]. The differential function of D1 receptors on pyramidal cells (1) and of D1 receptors versus D2 (D3/D4) receptors on inhibitory neurons (2) may generate "cognitive" functions (e.g. working memory) in the subcircuit between pyramidal cells that is based on reciprocal excitatory interactions (4). The self-inhibition of pyramidal cells (3) via GABA releasing inhibitory neurons (IN) and connections to dopamine cell centers (DA) in the mid brain (4, ventral tegmental area) and in Nucleus accumbens must also be taken into consideration for functional understanding, although there are still open questions.

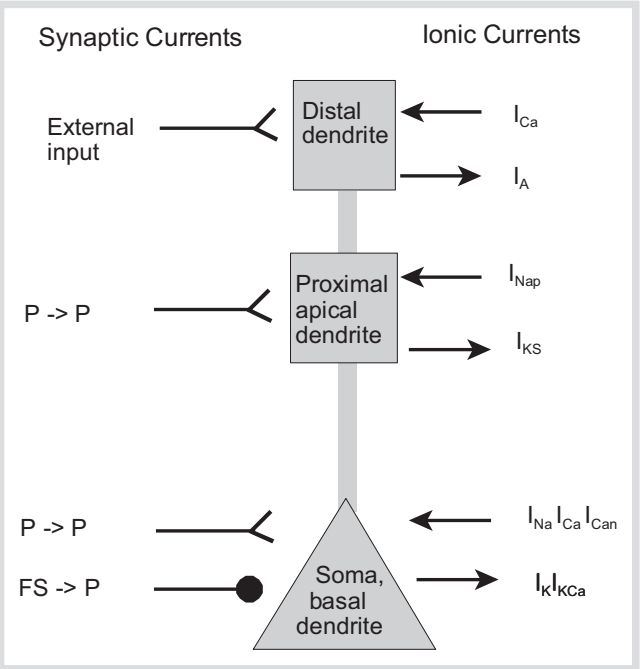

Fig. 12 Compartment model of the pyramidal cell [78]. P: pyramidal cell, FS: fast spiking (inhibitory) cell, I_{Ca}: calcium current, I_{Can}: calcium dependent cation current, I_A: transient A-type potassium current, I_{Nap}: sodium current I_{KS}: slow potassium current, I_K: potassium current, I_{KCa} : calcium dependent potassium current?

that – regarding environmental events – regulates down a "too much" as well as regulates up a "too few" of activity of the network. However, it is not clear what dopamine is "really" signaling in the brain.

Keeping in mind these unresolved issues, we would like to consider some models of working memory of PFC.

Models of the PFC network – some types of "canonical" circuits and their modules

Models of prefrontal cortical networks have to start with the formal conceptualization of the neurons, then it has to be decided about the functional structure of synapses and then the number of inhibitory and excitatory model neurons has to be determined. Building artificial network models with hundreds or thousands of neurons needs very much time and much computer power [comp. Vogels and Abbott (p. S73) in this issue]. Vogels and Abbott show that a relatively small population of excitatory and inhibitory connected neurons can generate complex behaviors. Only 20% inhibitory interneurons are usually used in network models. It is very crucial to design a multioptional structure of the modules.

Modeling the neuron

Every neuron in the network model must be designed in detail. For instance, the working group of Xio-Jing Wang [74] used Hodgkin-Huxley-type conductance-based models for single pyramidal cells and interneurons in order to maximize biophysical validity. The model neurons are calibrated by in vitro physiological measurements. Pyramidal neurons are modeled with three compartments, representing a soma/initial axonal segment and a proximal and a distal dendrite (**Fig. 12**). The functional characteristics were determined by specific properties of the kinetics of calcium, sodium and potassium channels and conductances with regard to their locations on the dendrites or on the soma of the cells. As can be clearly seen, even this sophisticated model ignores basal dendrites, although it does consider the topology of apical dendrites. But models can never map "reality" 1:1 - the appropriate selection of parts of reality as "significant" components can only be determined by the aim of modeling.

Network models

One of the successful network models with regard to implementation into theory of schizophrenia was constructed by Daniel Durstewitz and collaborators [25]. This model is based on the physiological finding that a low ratio of D1R to D2R might be a significant property of a "schizophrenic" prefrontal neuronal network. The modular structure of the network is based on an excitatory and an inhibitory neuron that are both reciprocally connected and exert lateral excitation and inhibition to other modules of the network (**Fig. 13**).

Also by Gustavo Deco and his group a network model was constructed that is specially adapted for the current PCF issue [Loh et al. (p. S78) in this issue, comp.22].

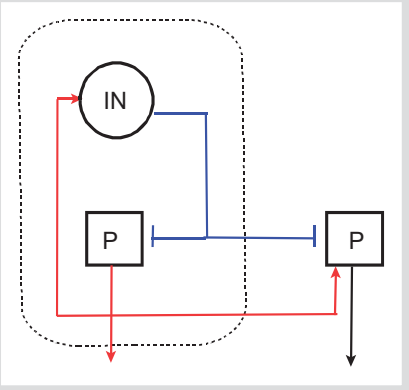

Fig. 13 Basic structure of the module of the artificial neural network model used by Durstewitz et al [25]: Structurally, the self-inhibition and lateral inhibition and lateral activation might be significant for the functional network properties [modif. from 25].

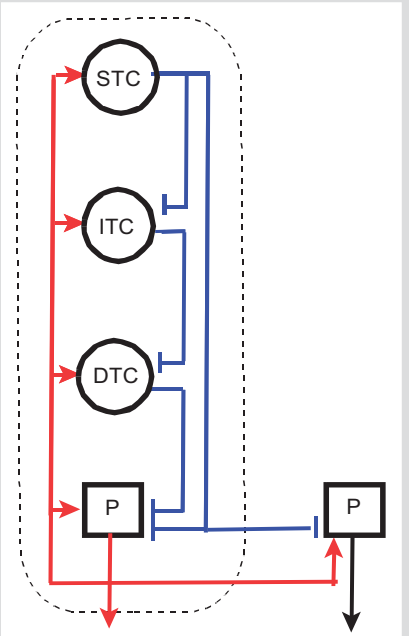

Fig. 14 Module of articifical neural network model of Wang and coworkers [74]. The self-inhibition and lateral inhibition and activation might be significant for the network properties with three types of inhibitory neurons. IN: inhibitory neuron, P: pyramidal cell, STC = perisoma-targeting PV cell, ITC = interneuron-targeting CR cell, DTC = dendrite-targeting CB cell (comp. **Table 2**).

Another model was constructed by Xio Jing Wang and his collaborators [cf. 18, 72,74, 75]. This model helps to understand disorders of visuospatial working memory on the basis of local prefrontal cortical circuitry and will now be described in detail. It's modular structure is more complex then other PFC network models and it can simulate a lot of properties of real PFC networks. The significant feature of this model is that three populations of inhibitory neurons are integrated in the concept [10,65,72]. This network model is based on several hundreds of activating neurons (512 pyramidal neurons) and more then one hundert inhibiting neurons (64 CR neurons, 32 CB neurons, and 32 PV neurons). The neurons are spatially distributed in a ring according to the preferred visual stimulus cues (0–360°). The strength of the recurrent connections between neurons in the network depends on the difference between their preferred cues. The recurrent excitatory input to pyramidal cells is provided by slow signaling NMDA receptors. All neurons receive unspecified external excitatory inputs mediated by fast signaling AMPA receptors.

The activity of selectively activated pyramidal (P) cells (here: "P cells") recruits CR neurons (ITC) with similar preferred cues. These neurons target CB neurons (DTC), so that activation of CR neurons then increases inhibition transmitted to dendrite-targeting CB neurons likewise tuned to similar preferred cues and thereby reducing CB inhibition on P cells during the delay period. On the other hand, on the flanks of the bump, the enhanced activity of perisoma targeting PV interneurons (STL) suppresses CR cells and CB neurons consequently receive reduced inhibition from CR cells (possibly also increased excitation from P neurons): They therefore fire at higher rates during the delay period during an experimental working memory task (s. below). The end result is that CB interneurons send enhanced inhibition to those neighboring P cells that are selective to other stimuli. This corresponds to the principle of lateral inhibition.

Simulation of working memory functions – the role of dopamine

Computational modeling should reproduce experimental data under various conditions. This can be demonstrated with the model of Wang and his coworkers. The basis of this model are data form a paradigmatic experimental animal model of working memory function as it was established by Patricia Goldman-Rakic and her collaborators [eg. [s. 26, 27, 28, 29, 30, 72, 73]: In monkeys, at spatial working memory tasks a persistence of stimulus-induced neuronal activity can be recorded in the dorsolateral PFC. In these experiments, the monkey is looking to a fixation point and laterally a cue is presented briefly. Then the monkey has to fixate for several seconds. Afterwards he should look to the spot where the cue was presented and he will obtain juice for reward (**Fig. 15A**). Electrophysiological recordings show that PFC neurons have a raised level of activation persisting during the delay period. This persistence of neural activity of pyramidal neurons might correspond to the working memory function.

Wang and his group could reproduce the procedural structure of this experimental situation and the discharge pattern of the neurons by their computerized model (**Fig. 15B**); [74]. They simulated dopamine D1R-mediated influences on the network of various strengths. This was performed by assuming that dopamine modulates the NMDA transmission, as has been shown by experimental data [48]. They found the inverted u shape of function of working memory, depending on D1R modulation of NMDA receptors in pyramidal cells and interneurons (**Fig. 16**). Interestingly enough, recent work suggests that D1R activation in fact increases the ratio of dendritic/somatic inhibition onto P cells in the prefrontal cortex [28]. Dopamine was found to reduce the efficacy of inhibitory synapses onto the perisomatic domains of a P cell. This is mediated by fast-spiking interneurons (FS, PFC, PV). On the other hand, dopamine enhances inhibition at synapses from accommodating or low-threshold spiking interneurons (CB, DTC) that target the dendritic domains of a P cell [28]. In Wang's model, according to the disinhibition mechanism, dendritic inhibition is reduced locally in activated P cells and increased in those P cells not engaged in encoding the shown stimulus. The simulations suggest that this mechanism is mediated by CB interneurons and might serve to filter out distracting stimuli, thereby rendering memory storage robust. Wang et al. showed that this mechanism is enhanced by a higher dendritic/somatic inhibition ratio, which could be hard-wired or dynamically controlled by neuromodulation [74]. The model predicts a specific function for such a dual dopamine action: it might boost the ability of a working memory network to filter out behaviorally irrelevant distracting stimuli. Obvi-

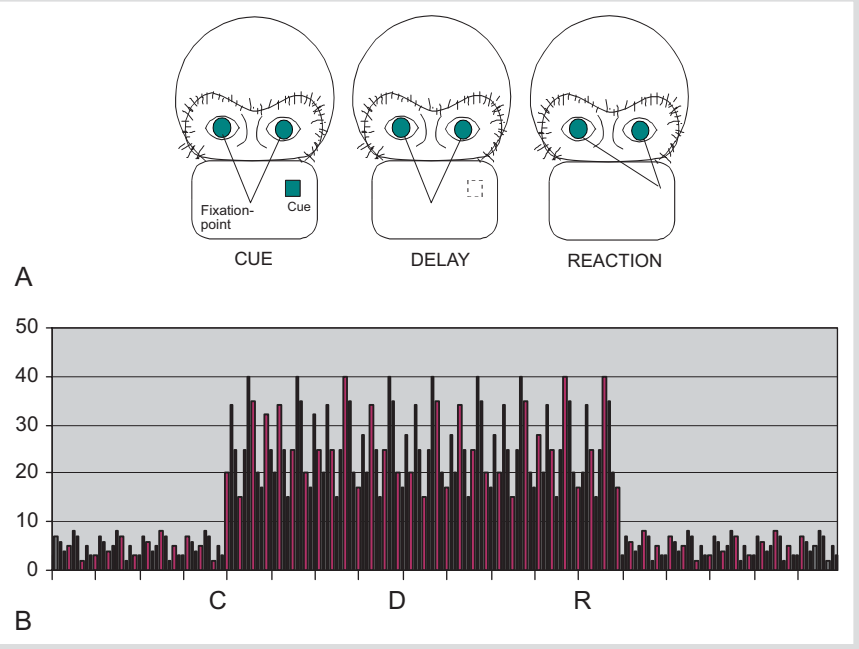

Fig. 15 Scheme of experimental setting for neurophysiological testing of visual working memory function. The monkey must fixate although a cue is presented briefly. The animal has to memorize the location of the cue and after a brief delay period the monkey has to look to the location of the cue and will receive a reward (**A**). Simultaneous recordings of neuronal activity show a raise of discharge frequency during the delay period (**B**). This pattern can be reproduced by experimentation by computational PFC network models [modif. from 77].

ously, a strongly recurrent microcircuit is stable if the reverberation is mediated by slow NMDA-based excitation [16,65].

This model also suggests one possible scenario for the way in which impaired dopamine modulation of PFC might lead to working memory deficits and abnormal distractibility in schizophrenia. These findings correspond to the results of simulations with the model of Durstewitz and coworkers [25; s. also 24]. It should be mentioned here, that additionally gamma-oscillations were generated in simulated cognition experiments performed with this network model.

Summarizing his computer-based "in-silico" experiments, Wang states that the interplay between slow reverberating excitation and competitive synaptic inhibition enables a cortical area, such as the prefrontal cortex, to subserve various cognitive functions.

Next steps – synopsis of complexity of (dopaminergic) synaptic neurotransmission

For more detailed computer-based studies of receptor effects, in an integrative approach some further aspects have to be determined by experimental research. Up to now, we have no appropriate model of the dynamics of the (dopamine) synapse. Still the dynamics of the various interconnected mechanisms such as release, activation of reuptake, effects of autoreceptor activation (**Fig. 17**), etc. is not yet fully described and of course, not understood [54]. Data on synaptic transmission show that the switch from electrical signaling to chemical signaling and back to electrical signaling is not yet fully analyzed [3,71]. Synapses may function not only as simple transducers, as in many cases there is no 1:1 transmission [3]. Synapses even might work as little processors, as they can exert filter operations, as Larry Abbott and his group have demonstrated [3]: Postsynaptic cells may respond to slow frequencies better than to high frequencies (low pass filter) or vice versa (high pass filters), or they may respond maximally to a certain frequency (band pass filters). D1 receptor-based synapses might thus operate like low pass filters and D2 receptors might be high pass filters.

Some questions, that should be answered in a neuronal network perspective are:

- When do D1 vs. D2 receptors activate or inhibit the respective cell? At present, from an electrophysiological point of view, a consistent dichotomy of activating and inhibiting effects of dopamine receptors can not be drawn any more as it is known that the effects depend on the membrane potential, on the location of the receptors on the cell etc. [24,55; DiPietro and Seamans (p. S27) in this issue].
- Which neurons – excitatory or inhibitory - show a functional dominance of D1 receptors? For instance, inhibitory neurons express both types of receptors but maybe in fast spiking neurons mainly the D1 receptors are functionally relevant [72,73].
- What is the normal or default state of the neuron in electrophysiological terms (up-/down-state, spontaneous activity, discharge rate/pattern)?
- Where are the functionally dominating receptors located on the cell and in and around the synapse? Receptors on apical dendrites exert other electrophysiological properties then those that are located on the soma of the neuron [76,77]. Also intrasynaptic, presynaptic and postynaptic receptors show different behavior. For instance, extrasynaptic receptors and also extrasynaptic release sites are now increasingly regarded as important sites of transmission [14]. Also the location of the receptors on the cell are of importance as dendritic D1R differentially reduce somatic inhibition and enhance dendritic inhibition onto pyramidal neurons [28] (comp. **Fig. 14**).
- What are the kinetics of the concentrations of dopamine? This is interesting as extrasynaptic concentrations show very slow kinetics compared to intrasynaptic dynamics [14]. The time course of transmitter concentration seems to be very smooth – it take seconds after an arriving burst of action potentials that the dopamine concentration is normalized again [54].

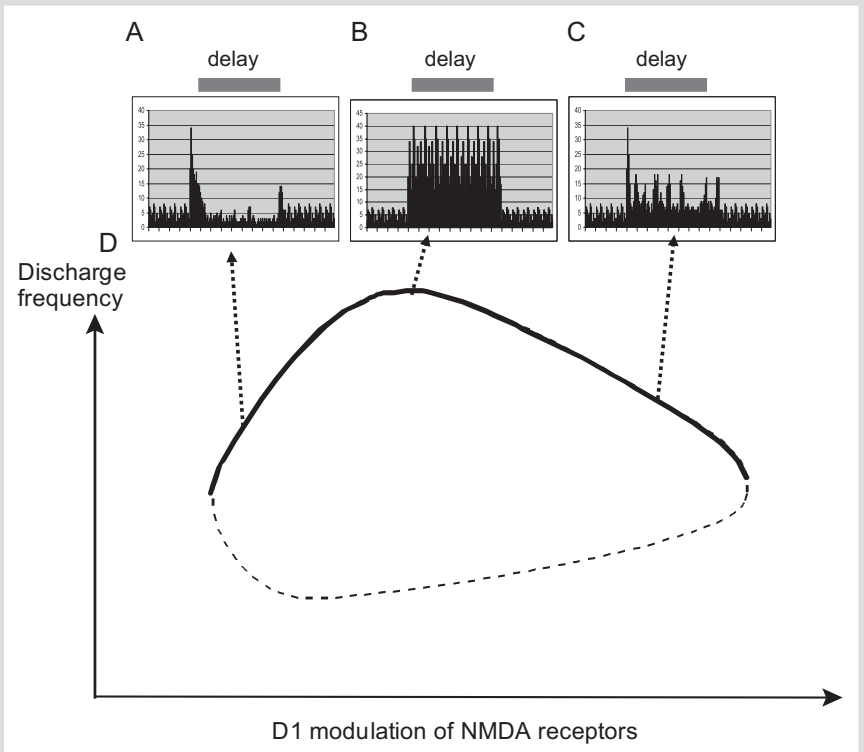

Fig. 16 Simulation of working memory task under various conditions. Scheme of validated simulation of neuronal computation of weak, stable and instable working memory function depending on the D1 modulation of NMDA receptors [modif. from 10, 75, 76, 77]. (**A**) Low persistent neuronal activity at low D1R modulation, (**B**) high persistent activity at medium D1R modulation and (**C**) low persistent activity at high D1R modulation resulting in a Inverted u-function on the phase portrait of the attractor (**D**). The bifurcation diagram shows that persistent activity is highest in an intermediate range of D1 receptor activation.

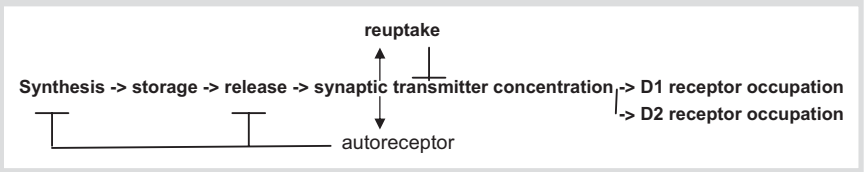

Fig. 17 Synaptic transmission and structure of processes with feedback loops with inhibition on transmission (arrows with transoms = inhibition).

- What is the dynamics of the reactivity of the various receptors depending on the duration of stimulation (up-/down-regulation, sensitization, desensitization)?
- Finally, the differential functional evaluation of (cortical) phasic active projections from the ventral tegmental area (VTA) as bursts, being composed of about 5 spikes with 15 Hz (about 70 ms inter-spike interval), and of (subcortical) tonic activity from substantia nigra (SN) to the striatum (STR) with a low sustained-frequency pattern (4 Hz, about 250 ms inter-spike interval) should be considered, as observed and analyzed by Grace, O'Donnell and others [32, 49–51].

These questions are related to the aim of "naturalistic" modeling of neuronal networks.

Additionally, in order to understand the effects of antipsychotic medication on the entire cellular level, a model must be built that integrates current insights into molecular intracellular signaling pathways and their functional interconnections.The focus would be the adaptation of receptors after chronic administration of drugs. For schizophrenia, for example, the intracellular dopamine signal transduction is already too complex to be understood entirely without computer simulations. Also adaptation of D2R function after chronic application of antipsychotic drugs is not yet fully understood. Also the interconnections with the molecular pathways of other transmitter systems like GABA and glutamate should be studied in a systems perspective.

A systemic approach already is established in microbiology and now is starting in the molecular and biochemical study of mammalian cells. This approach is named "Systems Biology" [40]. It will open a new understanding of pharmaceutical actions by reconstructing the cell on the computer. This will allow for "in-silico" experiments on the computer. If Systems biology, that is concerned with chemical signaling, meets Computational neuroscience that is concerned with electrical signaling a fruitfull multi-level-understanding of the nervous system, the disorders and the mechanisms of pharmacotherapy seems to be possible. With this aim we organized a workshop in spring 2007 and we would like to mention already here, that in the next publication on Computational Systems Neuropsychiatry we will report on the Systems Biology perspective that is devoted to mechanisms in intracellular dopamine signaling networks in Schizophrenia and related issues.

Conclusions

Proper understanding of the brain processes involved in schizophrenia (and other mental disorders) should be related to signaling networks at several levels of cerebral information processing. In this systemic view of a Computational Systems Neuropsychiatry, the pharmacological perspective must also take into account the synaptic organization of the neural circuitry with regard to the distribution of receptors like D2 receptors. However, modeling of cerebral circuits on the molecular level implies a selection of available data and knowledge in

order to construct not too complex models. The conceptual selection of substructures of a certain cerebral network must be made more explicit so that communication between theoreticians and empirical researchers is close enough. Modeling neural circuits requires an explicit methodology that allows for interdisciplinary communication. For understanding complex neurobiological "wiring diagrams", computer-based modeling and computer simulations must be used. Although computational neurobiology already has provided several convincing models they must be adjusted to neuropsychiatric issues. Consequently, a field of theoretical neuropsychiatry (Computational Neuropsychiatry) should be established in order to develop theories of mental disorders in a systematic way. This field should be developed by integrating the knowledge of systems science. Several stimulating models of disorders of working memory or perception are already published. These approaches should be improved by interaction with clinical researchers and practitioners. The need for systemic modeling becomes evident if the difficulties are regarded that arise when the functional role of D1 and D2 receptors has to be determined on a theoretical level. Especially, the superimposition of several inhibitory circuits in the cortex have to be studied analytically. Therefore, theoretical modeling that is integrating classical computational neuroscience with molecular systems biology will be a challenging task for neuropsychiatry for the next years.

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