From The Department of Neurobiology, Care sciences and Society
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Aminergic Regulation of Neuronal Synchrony in the Hippocampus

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Abstract

Background
Gamma oscillations (25-80 Hz) are physiological electric activity patterns, prevalent in the brain, which are associated with attention, working memory, sensory perception, long-term memory encoding and recall. Importantly, in mental illnesses featuring cognitive disturbances (such as Schizophrenia or Alzheimer's disease) there are concomitant disturbances of gamma oscillations. All aspects of cognitive function are regulated by the aminergic systems of the brain, which are also associated with mental disorders. Yet little research has been done to understand how aminergic molecules modulate or control gamma oscillations.

Aims
We aimed to investigate whether gamma oscillations are modulated by aminergic G-protein-coupled receptors. We also wanted to determine which types of neurons and circuitry mechanisms are responsible for any aminergic effects uncovered.

Methods
We used an *in vitro* preparation of the rodent hippocampus in which stable gamma oscillations were elicited by the application of kainic acid. Combined extracellular local field potential and intracellular patch clamp recordings were used to reveal which network, synaptic and cellular parameters changed in response to various pharmacological challenges.

Results & Conclusions
We found that it is possible to bi-directionally regulate gamma oscillations in the hippocampus, without affecting the overall firing-rate of action potentials. Rather, it is the phase-synchronization of pyramidal cell and fast-spiking interneuron activity that is affected by histamine H3 and dopamine D4 receptors, respectively. This is a potential physiological mechanism by which the gain of signal transmission to downstream targets can be regulated. Targeting this mechanism may have a potential use in future antipsychotic or pro-cognitive pharmaceutical therapy.

I thought yesterday was the first day of the rest
of my life but it turns out today is...

Steve Martin

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Preface

List of Publications

This thesis has been written to fulfill the requirements of the doctorate of Medicine at Karolinska Institutet. The thesis is based on the following publications which will be referred to by the corresponding Roman numeral.

I. *Histamine H3 receptor activation decreases kainate-induced hippocampal gamma oscillations in vitro by action potential desynchronization in pyramidal neurons.* (2010) **Andersson R.**, Lindskog M. and Fisahn A. *Journal of Physiology* (588): 1241-1249.

II. *Neuregulin and dopamine modulation of hippocampal gamma oscillations is dependent on dopamine D4 receptors.* (2012) **Andersson R.**, Johnston A., Herman P., Winzer-Serhan U., Karavanova I, Vullhorst D., Fisahn A., and Buonanno A. *Proceedings of the National Academy of Science* (109)32: 13118-13123.

III. *Dopamine D4 Receptor Activation Increases Hippocampal Gamma Oscillations by Enhancing Synchronization of Fast-Spiking Interneurons.* (2012) **Andersson R.**, Johnston A. and Fisahn A. *PLoS ONE* (7)7: e40906.

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List of Abbreviations

ACSF	Artificial Cerebrospinal Fluid
ADHD	Attention-Deficit Hyperactivity-Disorder
AHP	After-Hyperpolarization
AMPA	(2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid)
CA	Cornu Ammonis
cAMP	cyclic Adenosinemonophosphate
CCK	Cholecystokinin
CNS	Central Nervous System
EEG	Electroencephalogram
EPSC	Excitatory Postsynaptic Current
ErbB4	Erythroblastic leukemia viral oncogene homolog 4
fMRI	functional Magnetic Resonance Imaging
FS	Fast-spiking Interneuron
GABA	Gamma-amino-Butyric Acid
GPCR	G-Protein Coupled Receptor
ING	Interneuron Network model of Gamma Oscillations
IPSC	Inhibitory Postsynaptic Current
KA	Kainic Acid
LFP	Local Field Potential Oscillations
MAPK	Mitogen-Activated Protein Kinase
MEG	Magnetoencephalogram
nFS	non-Fast spiking Interneurons
NMDA	N-methyl-D-aspartate
PET	Positron-Emission-Tomography
PING	Pyramidal cell-Interneuron Network model of Gamma Oscillations
PKA	Protein Kinase A
RAMH	R-alpha-methylhistamine
SNpc	Substantia Nigra pars compacta
VTA	Ventral Tegmental Area

Layperson's Introduction

All organisms have information processing needs

A fundamental problem for cellular organisms is how to gather information about their environment, interpret it (or at least sense some important features) and then act in order to achieve favorable outcomes. Such problems range from how to find nutrients, shelter and mates, when to be active and when to rest, how to compete with rivals etc. There are many strictly chemical or mechanical ways to solve these problems but it seems that a common set of electrical properties of cells are conserved across the branches of the tree of life.

The lipid bilayer membrane (a soap bubble-like arrangement of a double layer of fatty molecules) of the cell allows the establishment of electrochemical ion gradients. Tiny pores or channels in these membranes allow ions to pass it, a property necessary for establishing the gradients in the first place. The various channels have also evolved to allow the passage of ions in response to light, mechanical pressure, mechanical stretch, acidity, temperature and even voltage as well as a vast number of chemicals, thereby providing the cell with signals from the outside world. The dynamic regulation of the flow of ions together with the membranes ability to store charge allows the integration of signals and thereby more sensitive and measured responses to the events in the outside world. These properties have been used by the 3 major branches of life: archaea, prokaryotes and eukaryotes (that is from primitive algae and bacteria to yeast, plants and animals) to enable a rich variety of behaviors [1].

The nervous system is specialized for information processing by means of electrochemical signaling

The electrochemical properties are scalable to the information processing needs of multicellular organisms. In the animal kingdom,

specialized organs and cell types have evolved to sense the outside world, interpret it, learn about it, remember it and finally to produce behaviors. The nervous system carries the main responsibility for information processing and contains cells that are specialized for receiving and transmitting fast electrochemical signals. These are called nerve cells or neurons [2]. The neurons have widespread branches extending from the cell body, which connect one neuron to another, via specialized contacts called synapses, producing a complex network. Some branches are specialized for receiving signals that are then conducted to the cell body where they are integrated. As a result of the integration the neuron is then either excited enough to pass the signal forward or it is not. Once excited above a certain threshold the neuron produces a high amplitude transient spike in its membrane voltage. This is also known as an action potential, which then spreads across the branches of the neuron, in particular along the axonal branch, which is specialized for transmitting the signal to other neurons. At the synaptic contact points to other neurons the action potential produces a release of molecules that bind to the next neuron, modifying its activity. This simplified description of neuronal structure and integration omits the complexities arising from the multitude of different neuron classes, signaling molecules and modulation pathways. Contrasting this complexity is the fundamental nature of the action potential, which, stands out as the basic unit of neuronal signaling. The relative timing of action potential generation is the theme of two of the papers included in this thesis.

Rhythmic electrical activity in the brain seems to be important for our perception of the world

Rhythmic activity, that is the occurrence of repeated events with regular intervals, seems to be one of the core working principles of body organs using electric signaling. Breathing, the heartbeat, the peristaltic movements of the intestines and even walking are examples of this principle. Especially the brain exhibits a variety of rhythmic electrical activities in different frequency bands. In contrast to the aforementioned examples there is no firm consensus about the function of these brain rhythms. The brain is tasked with the problem of providing a seamless and coherent experience of the world combining the input of our senses with our own internal interpretation of what everything means. There appear to be a number of rhythms in different frequency bands associated with these tasks. One of these rhythms lies in the gamma-frequency band and is often referred to as gamma oscillations. All the papers included in this thesis are concerned with this particular brain rhythm.

We have chosen to investigate gamma oscillations in a part of the mammalian brain, the hippocampus, that is not directly involved in either the gathering of information from the senses or the activation of muscles. Rather the hippocampus seems to be concerned with organizing signals from almost all parts of the brain, integrating information across all sensory modalities, internal emotional and motivational states and even abstract concepts. The hippocampus seems to be essential for understanding contexts and relationships, recognizing patterns, navigating and importantly, formation of memories about events and facts about the world. Put in other words the hippocampus (and associated areas) are important for our geographical understanding of where we live, where the closest grocery store is from there and which the shortest path is to get there. Moreover the hippocampus is necessary for remembering what to get at the store. The hippocampus was necessary for us to learn the concept of a grocery store as a child, but not for learning how to ride a bike. Based on our previous experience with grocery stores we would be able to imagine what it would be like in a store we have never visited before. Another interesting feature of the hippocampus is its high level of neuronal organization in layers with a clear direction of the propagation of signals. Some of the hippocampal areas have many internal connections between neurons and can generate gamma oscillations. We have therefore chosen to carry out our experiments in these areas as an experimental model of the whole brain.

Psychiatric disease may be a result of disrupted rhythmical activity in neuronal networks

While there is no firm evidence showing that higher brain functions such as learning, memory and cognition are dependent on oscillations, there is however a considerable amount of data showing that gamma oscillations are at least associated with these functions. When subjects are asked to carry out tasks involving memory recall, face recognition, arithmetic problems etc. gamma oscillations are consistently found to be associated with these tasks. In addition, patients afflicted with psychiatric diseases, such as schizophrenia, have disrupted gamma oscillations. The hypothesis that aspects of schizophrenia are the result of disrupted gamma oscillations is very attractive to neuroscientists because it can potentially explain many disparate findings in schizophrenia patients, such as lower numbers of certain types of neurons, mutations in several unrelated genes, abnormal levels of neurotransmitters etc. Many of these findings can result in disrupted regulation of gamma oscillations. If the oscillations in turn are important for proper function of the mental faculties of the brain it is then possible to see the connection between a mutation in a gene, abnormal neuronal activity, disrupted gamma oscillations and the symptoms of schizophrenia.

The tools at the disposal of neuroscientists are still relatively coarse and it is difficult to selectively manipulate a particular neuronal property such that they stop synchronizing their activity amongst themselves but fire action potentials with the same responsiveness to a mental task. Certain drugs and abnormal levels of neurotransmitters are known to alter mental function. If gamma oscillations are activity patterns necessary for such functions one would expect the oscillations to be altered as well. Indeed we found that by applying drugs and neurotransmitters to slices of the rat hippocampus we can alter the degree of synchronous activity in neurons and the power of gamma oscillations, without substantial effects on the rate of action potential discharge. We believe that the regulation of gamma oscillation power is potentially useful for alleviating some of the symptoms of schizophrenia.

Introduction

Aminergic neurotransmitters regulate mental function

THE brain was understood to be an organ specialized in information processing by means of electrical transmission by the first decades of the 20th century. This view persists today, as theorists create models of the brain as a system of electrically interconnected nodes essentially performing "packet-routing" of signals [3]. While this view has merit at some levels of abstraction, it became clear by the late nineteen-fifties, following what was gleaned from neuropsychopharmacology, that a view of the brain as a strictly electrical organ does not completely explain the accumulating body of experimental data. According to the earlier view of the brain there were only fast synapses, i.e. either electrical synapses or fast chemical synapses with modified amino acid transmitters that would activate ion channels. The neurons would perform logic operations by integrating signals and then "decide" whether to pass the signal on or not.

One discovery of crucial importance for evolving our understanding of the brain was that dopamine is a neurotransmitter in its own right rather than merely a substrate in the noradrenaline synthesis pathway [4]. It generated a complementary understanding of brain information processing in the "chemical neurotransmission hypothesis" [5]. While this hypothesis was initially only concerned with the catecholamines it has now expanded to include a large number of peptides, amino acid transmitters, hormones and lipid mediators. The chemical neurotransmission hypothesis can be understood as a new level of complexity of the brain where slower signals are propagated by chemical mediators that act on receptors that activate signal transduction cascades of enzymes. The slow signal transduction cascades can then alter many parameters of neurons including gene expression, the sensitivity of synapses, efficiency of transmitter release, threshold

for, and patterns of, action potential discharge etc. [6]. This has been termed "neuromodulation", i.e. ligands that activate receptors coupled to enzymatic signal transduction cascades (also known as slow metabotropic transmission) that exert a modifying influence on the behavior of neurons without directly affecting the fast electric signaling. Moreover rather than being isolated to single synapses and neurons these slow transmitters can affect entire brain areas.

Dysfunction of slow chemical transmission is highly implicated in several disorders of the brain such as Parkinson's disease, schizophrenia, major depression as well as drug addiction. Exploring neuromodulation has advanced our fundamental understanding of the brain and yielded several clinically useful drugs such as L-Dopa, antipsychotics and antidepressants. This extra layer of complexity in signaling endows the brain with a range of capacities such as mood, alertness, emotion, mental focus, reward prediction etc [5, 7].

In order to provide examples of how the fast electrical signaling may interact with the neuromodualtory systems it is important to introduce the electrical signaling patterns that are believed to be important for cognition. A brief overview of schizophrenia will then be used as a framework for understanding how cognitive function can be disrupted when fast electrical signaling and neuromodulation are impaired. As certain types of neurons stand out as being highly implicated in schizophrenia they will also be introduced. Finally, the dopaminergic and histaminergic neuromodulation will be introduced as they were the subjects of the papers included in this thesis. This is followed by a discussion of the results focusing on the interplay between neuromodulation, gamma oscillations and the possible implications for cognitive function in schizophrenia.

Rhythmic electrical activity seems to be a basic mode of operation of the central nervous system

Rhythmic electrical activity (oscillations) has been found widely in the central nervous system (CNS) of mammals, including all cortical areas, cerebellum, thalamus, olfactory bulbs, basal ganglia, hippocampus, hypothalamus, retina, and several brain stem nuclei [8–15]. Because rhythmic activity is so widespread across areas and species it has been suggested to be inherent in the architecture of the central nervous system [16]. For the purpose of understanding oscillations the network can be said to have at least 2 levels of organization. The first level resides in the neurons themselves. It was recognized in Hodgkin's and Huxley's mathematical description of membrane potentials that sub-threshold oscillations can occur both as a result of excitation and inhibition of biological membranes capable of generating action potentials. And that this occurs as a result of the dynamic balance between the dominance of inward and outward

currents [15, 17]. The second level of organization is comprised of long-range or local excitatory connections and their counterbalance by local inhibitory connections. This local inhibition may slightly lag behind the excitatory input thereby producing initial excitation, increasing the probability of action potential discharge, followed by inhibition producing the opposite effect [15].

The frequencies of these rhythms vary across a large range, from rates little over 0 Hz up to 300 Hz. Reflecting the broadness of frequency ranges, there are hypotheses concerning a broad range of functions carried by electrical oscillations in the CNS. There is substantial understanding about the role of rhythms in the spinal cord with regard to the physiological functions of the organism such as locomotion. The hypotheses about the role of oscillations in the brain are still mostly based on correlative lines of evidence. Even though brain oscillations have been recorded in humans as early as the nineteen-twenties [18] the field of neurophysiology remains heavily engaged in the study of oscillations. Rhythmic network activity in the brain can be non-invasively recorded using electroencephalography (EEG) or magnetoencephalography (MEG). These types of recordings have been instrumental in establishing our hypotheses about the role of brain rhythms and helped categorizing them different frequency bands (very slow waves, alpha, delta, theta, beta, gamma and ripples) roughly reflecting different brain states. This has resulted in partially overlapping frequency bands with vague definitions that vary across species, brain areas and research disciplines – a fact that has to be borne in mind when comparing data recorded using different experimental paradigms.

Gamma oscillations are correlated with cognitive processes in the brain

Alterations of the EEG patterns across the cerebral cortex can be observed in patients undergoing general anesthesia before surgery. At the loss of consciousness the patients' brains undergo a marked decrease in oscillation power in the gamma-frequency band (i.e. 25-80 Hz) and increase of lower frequencies, notably in the delta frequency-band (1-4 Hz) [19, 20]. This seems to be a common effect of general anesthetic agents, which is reversed at the return of consciousness. Based on findings like this gamma oscillations have been associated with several functions such as long term memory encoding and recall [21], facilitation of synaptic plasticity [22], processing of visual and auditory stimuli [12, 13, 23], olfaction [11], maintenance of focused attention [23, 24], social function [25], perceptual grouping and pattern completion [26], working memory [27] and as an interface for information transfer between limbic and motor structures [10].

In addition to the mere presence of gamma oscillations in conjunction with various mental and perceptive faculties, there is evidence that correlates the magnitude of brain rhythmic network activity with the mental load of tasks associated with gamma oscillations. These include: working memory, attention and long-term memory recall or with the perceptive salience of sensory stimulation [11, 21, 23, 27–29]. Gamma oscillations have also been shown to have a relationship with the Blood Oxygenation-Level-Dependent signal in functional Magnetic Resonance Imaging (fMRI) [29, 30]. The fMRI signals are believed to reflect a neuronal process underlying or contributing to brain information processing relevant to cognitive function and are used extensively in cognitive and clinical neuroscience.

Taken together, there is a wealth of literature clearly indicating that cognitive function coincides with gamma oscillations in brain areas relevant to the cognitive faculty of interest. On the other hand little if any data exists demonstrating a direct causal relationship between gamma oscillations and brain information processing [16]. One can argue that the reason for this lack of direct data lies in the inherent difficulty in disabling the oscillatory synchrony in neuronal networks while leaving the synaptic connections and discharge-rates of the neurons intact.

Gamma oscillations enhance signal processing through neuronal synchrony

There is little fundamental mechanistic understanding of how rhythmic electrical activity in the brain underpins or contributes to information processing but it has been suggested that neuronal synchrony is what is gained by oscillations [15, 16]. Synchrony in this context refers to simultaneous membrane voltage changes among neurons [16]. Synchrony can occur by chance but will not last very long, neuronal oscillations on the other hand can impose and prolong synchrony in neuronal networks and it has been suggested that oscillations exert a form of top-down control in neuronal networks in anticipation of information processing needs [31]. The reason synchronized neurons can communicate more efficiently amongst themselves than un-synchronized neurons is because of the constraints imposed by membrane time-constants. Post-synaptic potentials can only summate in a time-window of a few tens of milliseconds before they dissipate [2]. For this reason, converging synchronized neurons are more likely to excite (or inhibit) target neurons than unsynchronized neurons. Also, if presynaptic excitatory neurons fire action potentials when post-synaptic neurons are also depolarized, the post-synaptic neurons are more likely to propagate the signal forward. By this logic it also follows that postsynaptic neurons are less likely to propagate unsynchronized presynaptic stimuli. Imposing

synchrony by oscillations is therefore a mechanism for increasing the signal-to-noise ratio [15, 23]. Experiments have shown that phase-synchronized stimuli of whiskers during ongoing artificial gamma oscillations elicited more precise and numerous post-synaptic spikes in the barrel field of the somatosensory cortex. Similarly, phase-synchronized stimuli during theta oscillations elicited substantially larger postsynaptic potentials than the unsynchronized stimuli [32].

Because the impact of synchronized groups of neurons is boosted it has been suggested that oscillations provide a function that can be likened to "carrier waves", which neuronal assemblies use to establish a functional coupling between each other [15]. When the brain processes sensory stimuli the various elements are processed separately in spatially disparate groups of neurons. The brain must then combine the processed elements into a coherent percept. This is called "the binding problem". The binding of these disparate groups of neurons by means of oscillations has been suggested to be the solution to this problem [12, 15, 23, 31, 33, 34]. Gamma oscillations can be observed a few hundred milliseconds after initial presentation with complex shapes. This induced oscillation was associated with a neuronal representation of visual percepts [35]. A complementary function of grouping neurons by oscillations is to route information flow through brain areas. Phase-synchronized neuronal assemblies can propagate their signals whereas unsynchronized ones cannot [36]. Because oscillations not only impose synchrony but also prolong this state, it has been suggested that oscillations are needed to maintain stable percepts after the sensory stimulus has abated [37]. Maintenance of activity on time-scales significantly longer than the membrane time-constant is also needed for the accumulation of "evidence" for making choices. Theta, beta and gamma oscillations have been shown to be involved in the gradual build-up and processing of pertinent neuronal activity in decision-making [38, 39].

Oscillations offer the possibility of encoding information in the timing of neuronal action potential firing in relation to the phase of ongoing oscillations [40]. Phase-encoding of information also makes it possible to store and replay sequences of neuronal firing. This enables neuronal circuits (particularly the hippocampus) to perform pattern completion and pattern segregation operations [36, 40, 41]. Lower frequency oscillations (i.e. theta and beta) can be found when different brain areas are involved in the same task. This has been hypothesized to be a mechanism to accommodate conduction delays [16] that arise in long-distance communication. Gamma oscillations however, have been suggested to be optimal for local area information processing because their period (15-40 ms) matches the membrane time constant for most neurons.

This match offers the optimal time-window for integration of postsynaptic potentials and hence binding of neuronal assemblies [12, 15, 22, 23, 31, 33, 34].

The hippocampus uses oscillations to process, memory, space and context

Much remains to be discovered about the function of the hippocampal formation. A few examples of its activity were presented here to highlight the relationship between gamma oscillations at a circuit level and the information processing demands of a larger brain structure. Because rhythmical activity is prominent in the hippocampal formation and deals with high-level information such as declarative memory, space and context it is an excellent area to study the neuronal mechanisms that underlie cognitive function. In order to carry out its functions the hippocampal formation must receive information from almost the entire brain. A brief overview of the functional architecture of the hippocampal formation will bring some perspective to the discussion before considering a few examples of how oscillations relate to the processing of memory, space and context.

The entorhinal cortex is the input and output structure of the hippocampal formation. The perirhinal and postrhinal cortices receive converging innervation from the cortical sensory areas; they in turn project to layers I, II and III of the entorhinal cortex. These layers of the entorhinal cortex also receive substantial innervation from olfactory areas. Afferents to the deep layers of the entorhinal cortex (IV and V) come from the medial prefrontal regions, anterior cingulate and retrosplenial cortices. A larger structural organization emerges where the superficial layers of entorhinal cortex receive sensory information whereas the deep layers receive "modulatory" input [16, 42]. Layers II and III of the entorhinal cortex project to the dentate gyrus and hippocampus proper. It has been suggested that within the hippocampus a topological organization is maintained. The septal levels of the hippocampus are mainly involved with "exteroceptive" information whereas the temporal levels are mainly involved with "interoceptive" information [42]. Information is integrated in CA1 and subiculum and projected forward to layers I,V and VI which are the output layers of the enthorhinal cortex. These layers of the enthorhinal cortex project back to neocortical and olfactory areas [16, 42]. Apart from the entorhinal cortex, the subiculum is the other primary output structure of the hippocampal formation. It projects to the anterior cingulate and retrosplenial cortices as well as nucleus accumbens, septum and mamillary complex. The anatomical organization of these macro-circuits are indicative of the notion of the brain not simply a network routing sensory signals to areas where motor commands are issued. It would be highly inefficient to send the

signals from the cortex around a long loop only to return to the cortex if the purpose was simply to find a path for the signals. If one instead takes the perspective that logic operations are performed on the signals, the hippocampal formation starts to seem more meaningful.

The gamma oscillations in the hippocampal formation are generated in either area CA3 or the entorhinal cortex [43]. The CA3 region, unlike CA1, can sustain its own rhythmic activity because of its rich system of recurrent excitatory connections and the strong perisomatic inhibitory connections [44]. The medial septum and CA3 have reciprocal connections and both structures exhibit theta and gamma oscillations. It is believed that oscillations in CA3 can be elicited by septal cholinergic, GABAergic, and perhaps glutamatergic input [45, 46]. As the recurrent excitation builds up in each cycle, increasing numbers of interneurons are recruited [16]. These neurons can counterbalance the excitation (thereby preventing epileptiform seizures) and they may also give rise to transient gamma oscillations nested within theta cycles [44]. The activity in CA3 is transmitted to CA1 through the Schaffer-collateral pathway. In this way the oscillations generated in CA3 can be imposed on the CA1 circuit [43]. There they are combined with inputs from the entorhinal cortex through the temperoammonic pathway. An interesting property of the CA1 pyramidal cells is that they can be triggered to fire by the temperoammonic input when it is properly phase-synchronized with the Schaffer-collateral input, otherwise the temperoammonic input is shunted [36]. This is an example of how theta oscillations can be used to perform Boolean logic "AND-operations" on a cellular level. Nested within the theta cycles are of course transient gamma oscillations (or perhaps more accurately gamma modulated firing sequences) that are also believed to be subject to combination and separation in CA1. The processed signals are then fed back into the subiculum and entorhinal cortex. Gamma and theta oscillations can arise independently of each other and while theta oscillations are most prominent during spatial exploration, gamma oscillations are most prominent during sensory stimulation (in particular sniffing in rats) [42]. In humans, hippocampal gamma oscillations are associated with working memory [21] and long term memory formation [47].

Classical studies of the hippocampus in humans showed that this structure was essential for memory formation. Patients with substantial damage to the hippocampi were rendered unable to retain new declarative information beyond the span of a few minutes [2, 48]. The hippocampal formation is also the structure where synaptic plasticity was first discovered [49]. This process has been suggested to be a cellular substrate for memory. With ongoing oscillations in the hippocampus, properly phase-synchronized synaptic impulses could be potentiated. As has been discussed earlier, this is because

oscillations can function as a mechanism of ordering and synchronizing the activity of neurons. Spike-timing dependent plasticity is enhanced by gamma oscillations because the oscillation cycle is a recurring time-window in which pre- and post-synaptic activity can be organized [22, 50–52]. While much about long-term memory remains to be investigated, it is possible that gamma oscillations play a role in long-term storage of information.

Another set of classical studies (mostly performed in rats) showed that the hippocampal formation is involved in spatial orientation [42]. This is accomplished on several levels, with crucial information converging on "place cells". These cells are typically recorded in hippocampus proper but can also be found in subiculum, pre- and parasubiculum and entorhinal cortex [42]. These cells encode discrete locations of the animal and can be combined under the influence of theta oscillations to produce a phase and rate-dependent code for the position and trajectory of the animal [53–55]. The place cells in turn receive input from "grid cells", which are found in layers II and III of the medial entorhinal cortex. The grid cells encode hexagonal grid patterns of the space, on top of which the "places" are mapped [42,56] Apart from the grid cells, environmental queues and information from "head-direction cells" feed in to the place cells. The anatomical distribution of the head-direction cells is not well-established but they have been found in several regions, notably anterior thalamus and dorsal presubiculum [42,57]. The place system relies on the head-direction cells to provide a directional framework for a representation of the environment in the hippocampal formation [42].

One interesting finding in humans relating to spatial orientation is that trainee taxi drivers in London, in the course of acquiring an internal spatial representation of the sprawling city also acquired an associated increase in gray matter volume in the posterior hippocampus [58]. Also emerging from human studies, is the view of the hippocampal formation as a structure involved with integrating sensory inputs with internal stored information to produce representations of "scenes" or contexts [59].

Studies of the hippocampal formation in humans underscore the importance of functions such as working memory, pattern separation, novelty detection, pattern-completion, error correction, signal amplification and representational functions. These functions are reported to be carried out in the hippocampal formation and to involve oscillations [16, 41, 59, 60].

Fast-spiking interneurons are essential for gamma oscillations

After having considered the broad layout of hippocampal functions, it is of interest to briefly review the role of the different types of neurons in the hippocampus in the generation and maintenance gamma oscillations. Apart from pyramidal cells and granule cells, it is not straight-forward to classify the various types of neurons in the hippocampus. As mentioned previously, it is clear that inhibitory neurons are necessary to generate gamma oscillations. Histological traits such as dendritic and axonal arbor extensions (e.g. "bistratified"), the location of the somata, expression of calcium-buffering proteins (e.g. "parvalbumin-expressing") and neurotransmitters (e.g. "cholecystokinin") are not always sufficient to account for the diversity of interneurons. For this reason one also includes physiological traits such as spiking patterns (e.g. "fast-spiking") or traits like synapse targeting patterns (e.g. "interneuron-targeting") [61, 62]. The various traits are not exclusive and the terminology is not unambiguous. An example is parvalbumin; this "interneuron marker" has been used successfully the last few years to identify and manipulate interneurons which express it and which are crucial for gamma oscillations. However, the interneurons expressing this marker are not absolutely homogenous as this group is reported to contain perisomatic targeting interneurons, axo-axonal cells as well as bi-stratified cells [61]. It is possible, but not always practical, to identify homogenous groups of interneurons by assessing the traits mentioned above and then grouping the neurons through a clustering-algorithm [63]. Throughout this text the interneurons will therefore be referred to using the same classifications as the cited authors used.

The importance of fast-spiking interneurons is founded on several key observations. One observation is that the pyramidal cells exhibit gamma-phased inhibitory post-synaptic potentials during ongoing gamma oscillations [43, 64, 65]. Strong rhythmic inhibition to the perisomatic region of pyramidal cells by perisomatic targeting fast-spiking interneurons (fast-spiking basket cells) is likely to drive this activity. Inhibition of the perisomatic and axon initial segment of the pyramidal cells carries substantial weight in regulating spiking patterns of pyramidal cells [64, 66, 67]. This is because the soma is a region where synaptic currents are integrated before being conducted to the axon initial segment where a "decision" is made by the neuron whether to fire or not. Strong inhibition at these places can therefore override excitatory currents from the dendrites [65]. Recently the regulation of the pyramidal cell axon initial segment has come under scrutiny as axo-axonic cells (a parvalbumin expressing GABAergic neuron-subtype, capable of firing at very high frequencies, yet is not phase coupled to gamma oscillations) have been shown to block locally

generated action potentials from back-propagating into the somatic region. Consistent with this, it has been shown that pyramidal cell axons, during gamma oscillations discharge at a rate of 4 or 5 time faster than the soma, likely producing substantially stronger phase-modulated excitation in the network than what has previously been believed [68]. Perhaps this is a mechanism for allowing efficient integration of synaptic input in the dendrites of pyramidal cells during ongoing gamma oscillations while limiting the interference of back-propagating action potentials by the partial segregation of its compartments. These findings underscore the importance of interneurons in regulating the integration and propagation of signals in neuronal networks.

The fast-spiking basket cells exhibit an action potential discharge pattern where action potentials occur in most cycles, tightly phase-coupled to the gamma oscillations [69]. The inhibitory currents in pyramidal cells are believed to contribute substantially to the LFP signal [43, 70, 71]. There is also a crucial role for fast-spiking basket cells in theta-gamma co-modulation where these cells fire bursts of action potentials. The bursts are paced at theta rhythm and within the bursts the action potentials are fired at gamma frequencies [72,73]. Taken together there are several lines of evidence showing crucial involvement of fast-spiking interneurons in gamma oscillations. The finding that driving parvalbumin-expressing neurons by optogenetic means, produces gamma oscillations [74] is perhaps the most decisive line of evidence. It causally links this class of interneurons to the generation of gamma oscillations.

There are two working models of the generation of gamma oscillations

While the crucial role of fast-spiking basket cells is well established there is still a debate over the role of other neurons, particularly pyramidal cells, in gamma oscillations. Broadly speaking there are 2 models for the generation of gamma oscillations: the interneuron network gamma model (ING) and the pyramidal cell–interneuron network gamma model (PING) [73].

Fast-spiking inhibitory neurons, induced to discharge in a synchronized and rhythmic pattern have been shown to be necessary and sufficient for the induction and maintenance of gamma oscillations [74–76]. This property emerges for several reasons. The fast-spiking basket cells are highly interconnected with each other [62, 77]. It has been shown that with strong enough excitatory drive, they synchronize their activity by virtue of their mutual inhibition and gap-junctions [77]. This takes place with a time constant dependent upon the kinetics of the $GABA_A$ receptors in inhibitory synapses onto the interneurons [73, 78]. Taken together, an interneuron network

gamma model is the minimal circuit needed to generate gamma oscillations if fast-spiking interneurons are provided with strong and phasic excitation.

In PING the interneurons provide the inhibition onto pyramidal cells thereby established timing-windows wherein the pyramidal cells are "allowed" to fire. An individual pyramidal cell may appear as if it fires in only about 5-10% of gamma cycles (as recorded from the soma) [69] but, as mentioned above, it may fire in as many as 20-50% of cycles as recorded from the axon [68], therefore they provide strong phase modulated excitatory feed-back onto the inhibitory neurons [43, 44, 70]. Pyramidal cells receive dominant synaptic inhibition rather than excitation during fast oscillations, whereas the opposite is the case in interneurons [70]. Strong synaptic excitation on to perisomatic-targeting interneurons recruits them into rhythmically inhibiting pyramidal cells whereby they contribute to the gamma oscillations [70, 79]. It then follows that excitation becomes rapidly counterbalanced by inhibition during ongoing network oscillations [80]. Taken together these findings would suggest that it is the interplay between interneurons and pyramidal cells in the CA3 recurrent system in terms of phase coupling and synaptic strength that regulate the amplitude of the gamma oscillations [43,65,70,71,79,80]. In other words, because interneurons and pyramidal cells provide mutual feed-back to each other and pyramidal cells have been shown to fire at a considerably higher rate than previously believed, we hypothesize that a pyramidal cell–interneuron network gamma model best explains physiological gamma oscillations.

After having considered the cellular mechanisms of gamma oscillations and their hypothesized role in cognition it is relevant to ask a few new questions:

- If gamma oscillations are important for cognition are the gamma oscillations disturbed or deficient in psychiatric disorders with cognitive impairments?

- If aminergic neurotransmitters are involved in both cognitive function as well as psychiatric disorders are they also involved in regulating gamma oscillations?

- If both pyramidal cells and fast spiking interneurons are important for generating and sustaining gamma oscillations can either cell-type be regulated to impact gamma oscillations?

More background will be given to these questions before they will be revisited again in the results and discussion.

Cognitive deficits are core symptoms of schizophrenia

Because gamma oscillations are closely associated with cognitive function it is interesting to consider neurodegenerative or psychiatric illnesses with concomitant cognitive deficits. Alzheimer's disease, epilepsy, Attention-Deficit Hyperactivity-Disorder and schizophrenia have all been reported to have disrupted gamma oscillations [81]. Schizophrenia has by far received the most attention and the results are the most consistent with regard to gamma band disturbances [82]. Moreover because of the extensive literature concerning the neuropsychopharmacology of this mental disorder it emerges as an essential focal point for this thesis.

The symptomology of schizophrenia is typically divided into 3 categories; positive, negative and cognitive. Positive symptoms are defined as traits not existing before the onset of the illness. Typically these include the most debilitating delusions and hallucinations. Negative symptoms refer to traits existing before the disorder that have been lessened. These are typically social withdrawal, flattened affect, avolition, anhedonia, apathy, poverty of psychomotor behavior and impoverished speech. Cognitive symptoms encompass deficits in attention, working memory and executive function. Patients suffering from schizophrenia will often report "disorganized thoughts". There are also deficits in sensory and perceptual information processing [27, 82, 83]. Importantly, it is the cognitive impairments rather than the positive symptoms that determine the long-term functional outcome (i.e. occupational functioning, ability to carry out activities of daily life and social attainment) for schizophrenia patients [84].

Interestingly, when subjects with schizophrenia are presented with an auditory signal, the evoked early response in the auditory cortex is decreased. In conjunction with these deficits there is also a decrease in magnitude as well as an increased latency of the event-related responses believed to underlie perceptive processes of stimulus evaluation, discrimination and salience detection [85–87]. Processing of visual information is also subject to deficiencies in schizophrenia, particularly in tasks, which require grouping of visual elements in order to form a complete conceptual representation of an image [26, 88]. In these tasks the long-range gamma- (and beta-) band synchrony between the occipital lobe and frontal lobe was decreased in conjunction with an increased time to response. Other purely cognitive functions are affected as well. One example is arithmetic tasks where normal subjects exhibit increases in gamma power in the left fronto-temporal lobe whereas schizophrenia patients exhibited either no increase or an increase in the right fronto-temporal lobe [28]. Moreover the psychomotor responses may also be subject to deficiencies [89]. In accordance with the role of gamma oscillations

in supporting sensory, perceptual and cognitive information processing, there are many studies demonstrating a disruption of gamma oscillations in schizophrenia patients in conjunction with cognitive symptoms. The cognitive functions where deficits can be detected include: focused attention, information processing and maintaining information in working memory, acquisition of declarative knowledge and reasoning [26, 82, 85, 88, 90]. In EEG and MEG comparisons between schizophrenia patients and unaffected controls an interesting pattern is emerging. It seems that in affected individuals during task-less rest (this is often the "pre-stimulus" condition), there is an elevation of gamma and beta power as compared to unaffected controls. In trials related to stimuli or mental tasks on the other hand, affected individuals instead show a decreased power of the response in these frequency bands [82, 87, 91, 92]. For this reason investigators are now distinguishing "background" gamma and beta band responses from "stimulus related" responses. Some have even discussed these phenomena in terms of signal-to-noise relationships [91]. Put simply, the diminished stimulus-related gamma band response, the "signal" in schizophrenia patients, is drowned out by the background "noise". This is likely an over-simplification but it at least helps us to distinguish these 2 different modes of operation in cortical areas.

The gamma disturbances and cognitive symptoms of schizophrenia can arise in childhood (between the ages of 7 to 13), years before the mental disorder fully manifests and are therefore not a side-effect of antipsychotic medication [82, 83, 90]. Antipsychotic therapy ameliorates the positive symptoms but does little to restore gamma synchrony or cognitive function [82]. Furthermore, it is interesting to note that even relatives of affected individuals may exhibit mild deficits [93]. Cognitive deficits occur before the full clinical picture of schizophrenia develops, are persistent during the treatment and determine functional outcomes in patients. An emerging view is therefore that cognitive symptoms, with associated disruptions of gamma oscillations are core features of schizophrenia [83, 90, 94].

Dopamine is heavily implicated in cognitive and "limbic" functions

Dopamine has been shown to have a major role in many aspects of brain function and disorders such as Parkinson's disease, addiction, Attention Deficit Hyperactivity Disorder and importantly schizophrenia. As the sheer volume of this research is so great it will not be possible to do more than briefly discuss the role of dopamine in cognition, particularly with regard to its role in the hippocampal formation and in the etiology and treatment of schizophrenia.

The discovery of dopamine in the brain ushered in an understanding of the importance of neuromodulation [5]. There was an early

recognition of the importance of dopamine in the seemingly unrelated dysfunction of motor control in Parkinson's disease [95] and the correlation between antipsychotic efficacy and dopamine receptor occupancy [96–98]. The anatomy of the dopamine system shows that the broad functions are segregated, which explains why this neurotransmitter can be involved in such diverse functions. Apart from minor local dopaminergic cell groups, the major brain nuclei responsible for dopaminergic transmission in the brain are the Substantia Nigra pars compacta (SNpc), tuberoinfundibular nucleus and the Ventral Tegmental Area (VTA) [7]. The substantia nigra and the tuberoinfundibular support motor and action-selection functions and hormonal functions respectively, whereas the VTA supports cognitive function (discussed further below). The VTA is the principal source of dopaminergic innervation to the olfactory tubercle, prefrontal cortex, anterior cingulate cortex, nucleus accumbens, amygdala, septum and of importance for this discussion, the hippocampus and entorhinal cortex [99, 100]. These structures form the bulk of the mesocorticolimbic dopamine system (these can be divided in a mesocortical and a mesolimbic system but because the two are interconnected, they will be considered as one system [101]).

There are 5 types of dopamine receptors in the central nervous system (D1-5), which are all part of the G-protein coupled receptor (GPCR) family. These receptors regulate the activity of adenylate cyclase and thereby the levels of the second messenger cyclic adenosine-mono-phosphate (cAMP). The second messenger, in turn, regulates the downstream signal transducer cAMP-dependent protein kinase (PKA). Active PKA has extensive effects in neurons, regulating aspects as diverse as transcription factors and ion channels. The D1/5 receptors stimulate the activity of the adenylate cyclase whereas D2/3/4 receptors inhibit it [7]. The signaling can be rendered more diverse because of alternative splicing of the D2 receptors (short and long forms) and polymorphism of the D4 receptor, as well as potential formation of homo- and heteromeric receptor complexes [102], where dopamine receptors may engage signaling cascades usually reserved for other receptor classes.

Dopaminergic transmission of the mesocorticolimbic system is intricate with many disparate functions including: working memory, long-term memory, selective attention, learning, wakefulness, planning, goal-directed behavior, and choice evaluation [103]. Because the association between gamma oscillations and attention as well as the association between dopaminergic transmission and attention are well established, it has led to the conjecture that dopamine regulates neuronal properties that support or contribute to beta and gamma oscillations, which in turn support or contribute to attentive behavior. An example of this association was demonstrated in an experiment

where bilateral lesions of the VTA (in cats) produced the loss of beta and gamma oscillations in parietofrontal areas in conjunction with a loss of attentive behavior [104].

The mesocorticolimbic system is also involved in motivational drive, habit-formation, aversive-learning and encoding "reward prediction" [105]. However with the disruption of the dopaminergic system as with substance-abuse or in certain mental disorders such as schizophrenia, goal oriented behavior becomes compromised [91] and psychosis can ensue with excessive levels of dopamine. The relationship between dopamine concentration and cognitive functions has been likened to an "inverted-U-shape" [106]. In the lower concentration range there is a positive correlation between dopamine concentration and mental acuity and goal-directed behavior. At some point however there is an optimum and rather than saturating there, the higher concentration ranges are negatively correlated to cognitive function, where stereotypies, thought disorder, and hyperactivity can occur [103]. Initially it was only the level of D1 receptor activation and the outcomes in spatial working memory tasks that was demonstrated to have an "inverted U" relationship [106] but dopaminergic transmission and cognitive function in general seem to have the same characteristics [103].

Dopamine regulates the flow of information in the hippocampal formation

The hippocampal formation together with the nucleus accumbens, ventral pallidum, VTA and the prefrontal cortex constitute the "hippocampus-VTA loop". These structures have mutual direct or polysynaptic connections where information can be refined through an iterative process [103, 107]. Dopamine acts at all levels in this circuit and has been shown to have important effects in the hippocampal formation [103]. This structure receives the majority of its dopaminergic input from the VTA (although a minority of fibers also originate in SNpc), where the temporal part of the hippocampal formation receives more afferents than the septal part [100]. Dopamine has several functions in the hippocampus including novelty detection, encoding cognitive salience, and regulating learning and memory [103, 107, 108]. Dopamine signaling through D1/5 receptors has been shown to enhance and stabilize synaptic potentiation in the Schaffer-collateral pathway, as well as the hippocampal–prefrontal cortex pathway [101, 109, 110]. The dopamine D4 receptor, in contrast, is involved in reducing and reversing synaptic potentiation in the Schaffer-collateral pathway [111, 112].

Dopamine also "gates" entrant information flowing from the entorhinal cortex to CA1 through the temporoammonic pathway [113, 114]. The gating involves a mechanism where there is presynaptic inhibition

of glutamate release from temporoammonic fibers. It has been suggested that dopamine, by this mechanism, can control which signals from the entorhinal cortex are to be integrated with CA3 input in CA1. Dopamine has also been shown to "gate" input from the prefrontal cortex to area CA1 [113]. The effects elicited by dopamine were dependent upon both D1-like and D2-like receptors and could only be fully blocked with the antipsychotic drug clozapine, suggesting a possible role for the D4 receptor as well [113]. The regulation of synaptic plasticity and temporoammonic gating are putative mechanisms by which the hippocampus-VTA loop facilitates or inhibits the flow of information to CA1. As mentioned previously, information is integrated in CA1 and transmitted to the output structures of the hippocampal formation and then to other parts of the brain [36, 42, 113]. The hippocampus-VTA-loop is hypothesized to be particularly important in processing novel information, where dopamine in the hippocampus contributes to cognitive salience, psychomotor drive for exploration, and long-term storage of information [107]. Much remains to be discovered, but it provides an interesting framework around which one can design experiments. It is also interesting to consider what happens to this circuit in schizophrenia where cognitive function is compromised. One study suggests that aberrant positive feedback in a larger loop also containing the thalamus is involved in the development of the full onset of schizophrenia [115].

Antipsychotics are dopamine D2 receptor antagonists

Because the cognitive deficits in schizophrenia are core features of the disease and dopamine is heavily involved in regulating cognition it is of particular importance to review the role of dopamine in schizophrenia [82, 91, 116]. There are several findings that offer support for a principal role of dopamine in schizophrenia. Schizophrenic patients are supersensitive to drugs that elevate dopamine levels such as amphetamine, and when given in sufficient amount to healthy individuals these drugs elicit psychotic symptoms. Dopamine depleting drugs such as reserpine have an anti-psychotic effect [103, 117, 118]. In line with these findings, dopamine terminals in schizophrenic patients have been shown to have increased synthesis, storage and release of dopamine [119]. Finally, the fact that all effective antipsychotic drugs are D2 receptor antagonists (or weak partial agonists) is perhaps most important [96, 97, 118].

Antipsychotics are divided into 2 classes; typical and atypical but these classes are not stringently defined. First generation antipsychotics (also known as typical antipsychotics) were all potent D2 receptor antagonists. This pharmacological profile is effective against positive symptoms but it leaves the negative and cognitive aspects

largely untreated. Moreover, these pharmacological agents also produce extra-pyramidal side effects (i.e. motor side-effects) as well as neuroendocrine side effects [7]. Because of the possibility of side-effects at higher D2 receptor occupancy much effort has been made to find optimal dosing, where an antipsychotic effect is achieved (typically above 65-70% occupancy of brain D2 receptors) and where severe extrapyramidal and neuroendocrine side-effects are avoided (typically below 80% occupancy) [120]. Second generation antipsychotics (also known as atypical antipsychotics) proved to be more efficacious in many instances (particularly with "treatment-resistant patients"). Generally, the atypical antipsychotics have less extra-pyramidal side effects (although there are exceptions such as risperidone). The prime example of this class is clozapine. Its pharmacological profile is very complex and it seems to bind to a great variety of GPCRs apart from dopamine receptors including: muscarinic-, histaminergic-, serotinergic- and alpha-adrenergic receptors [7]. The fact that clozapine exhibits relatively low occupancy of the D2 receptors at clinically-used doses has sparked considerable interest in identifying which factors in its pharmacological profile produce the antipsychotic effect [121]. Because the understanding of the differences between typical and atypical drugs is far from complete, it has been suggested that a few relevant parameters should be highlighted. These include: where in the brain the ligands are binding, when the ligands bind, how long they stay there, how potent and efficacious are the ligands at the receptors and whether there are other classes of receptors being regulated [120].

How long the ligand binds to the receptor is known as kinetics of ligand dissociation, also known as "off-rates" of the antipsychotics. A high "off-constant" would then allow more of the phasic dopamine transmission and less of the tonic, potentially restoring the balance between these modes of transmission [122]. The efficacy of ligands has also been considered in the development of antipsychotics. As an alternative to low affinity antagonism (as in clozapine) a high affinity partial agonist, aripiprazole was developed [123]. In the face of the hypothesized hyperactive D2 receptor signaling in frontal and temporal areas, the two different mechanisms may produce a sufficient decrease to ameliorate positive symptoms, but both strategies leave sufficient D2 receptor-mediated signaling in the basal ganglia so as not to elicit strong motor-related side effects [118].

Where in the brain the ligands elicit their effects has also been a focus of interest. Tonic D2 receptor activation in the prefrontal cortex has been suggested to attenuate activity there whereas phasic D1 receptor activation in the hippocampus favors increased hippocampal activity [103]. D1 receptors also activate the prefrontal cortex but whether there is an increase or decrease of the activity of this receptor in frontal

areas in schizophrenia patients is unclear [103]. If the conjecture stating that tonic D2 receptor activity attenuates prefrontal activity is correct, it would also suggest that high "off-rate" kinetics for D2 receptor antagonists, or low affinity antagonism, restore the balance between prefrontal and hippocampal preeminence. It may also imply that one should look to other receptors that may influence the activity of the hippocampus and the prefrontal cortex.

Dopamine D4 receptors are involved in cognition

The D4 receptor came into focus when clozapine apart from its weak affinity to D2 receptors, was shown to have a moderate affinity for D4 receptors, where it acts as an antagonist [124]. Moreover, post-mortem findings in patients with schizophrenia indicate that D4 receptor levels are increased as a result of the disease rather than by drug treatment, as this finding was present in both medicated and un-medicated patients [125, 126]. The expression of this receptor seems to be the highest (in humans) in the hippocampus, medial temporal cortex and frontal areas of the cerebral cortex, whereas there is lower expression in other areas of the cerebral cortex, thalamus and caudate and putamen [126–130]. The localization of D4 receptors in rodents is still a matter of debate [131, 132]. Histological studies in primates indicate that the D4 receptors are expressed primarily in GABAergic interneurons [128], where they might be in a position to regulate rhythmical network activity. A potentially important aspect of the D4 receptor gene DRD4 is its genetic heterogeneity [133, 134]. The third intracellular-loop of the D4 receptor protein has a variable number of repeats of a 48-amino acid sequence, which occurs 2-11 times [135]. Polymorphism in these repeats (particularly the 7-fold repeat) is associated with ADHD, novelty-seeking and increases of gamma oscillation power [134–137]. Several studies using different pharmacological agents concluded that D4 receptor antagonism did not produce effective antipsychotic action, at least not with regard to positive symptoms [138–140]. It seems however that blocking the D4 receptor can ameliorate the cognitive deficits produced by phencyclidine in monkeys [141], whereas the inverse was shown in rats [142]. In general, reports have been more contradictory in rodents than in primates, where both agonists and antagonists of the D4 receptor produce enhanced cognitive performance [143–145]. In mice with genetically ablated D4R function there is decreased locomotion and behavioral response to novelty whereas increased locomotion in response to drugs of abuse were shown [146]. Detailed studies of the potential D4R-mediated effects on cognition in humans have not yet been carried out, although is has been suggested that the D4 receptors potentially regulate cognition and attention [147].

Because behavior is complex, some studies have instead focused on the effects of D4 receptor activation on physiological parameters such as synaptic plasticity. The D4 receptor has been shown to regulate long-term synaptic potentiation (LTP) in the CA1 area of hippocampus in mice [111, 112]. In regulating LTP the D4 receptor was shown to interact with Neuregulin-1 signaling [111] and the NR2B subunit of NMDA receptors [112] both of which have been implicated in the development of schizophrenia [82, 91]. Thus while investigating the role of the D4 receptor in animal models of cognitive deficits induced by phencyclidine the potential D4-NMDA receptor cross-talk should be borne in mind [112, 142, 148]. D4 receptor knock-out mice have enhanced NMDA and D1 receptor expression [149], suggesting that D4 and NMDA receptors could be functionally coupled and regulated together. There are however conflicting results suggesting that the D4 receptor mainly regulates $GABA_A$ or AMPA receptors in the prefrontal cortex [150, 151]. To better understand the role of the D4 receptor in plasticity, it is important to find intracellular mechanisms by which this receptor acts. Furthermore its effects on neuronal networks require elucidation, such that reasonable doses and behavioral paradigms can be used when D4 receptor pharmacology is investigated in intact animals. Even though there is no clear link between the D4 receptor and schizophrenia it seems that this receptor is involved in a variety of cognitive functions such as selective attention and working memory which may be subject to deficiencies in both schizophrenia and ADHD. Because of its enrichment in the medial temporal lobe and the prefrontal cortex, it is of interest to investigate possible mechanisms by which D4 receptor ligands could regulate activity there while leaving the basal ganglia unaffected.

Histamine is a neurotransmitter

Histamine is a polyamine transmitter-substance that is most abundant in mast cells and basophils circulating in the blood. In these cells the transmitter is stored in granules that are released upon antigen stimulation of membrane receptors. Released histamine regulates the immune response, vascular permeability and tone. Another prominent effect of histamine is that it induces itch, urticaria, sensitization of nerve endings and constriction of the airways. Histamine has several other important physiological functions in the periphery such as gastric acid production, excitation of enteric neurons and cardiac output [7, 152]. Because of its diverse action in the periphery it is perhaps not surprising that histamine, like serotonin, is a transmitter in the brain.

Because antihistamines (i.e. H1 receptor antagonists used to counter the effects of allergic responses) [7] produce sedation effects as a side-effect investigators explored the putative function of histamine

receptors in areas of brain that control wakefulness. The dorsal hypothalamus is crucially involved in wakefulness and this region also contains the tuberomamillary nucleus, which is the origin of histaminergic fibers in the CNS. From this location, histaminergic axons project extensively to almost all areas of the brain [153]. Interestingly, fibers form the supramamillary and tuberomamillary nuclei project directly to the pyramidal cells of ventral CA3/2 [154]. In spite of converging evidence from neurological and histological lesions, pharmacology and biochemistry, histamine took a long time to gain acceptance as a neurotransmitter in the neuroscience community [152]. The initial skepticism was based on 2 observations. First, circulating mast cells in the blood constitute the major source of histamine in any organ. It was therefore a matter of debate whether there were cells in the brain producing histamine endogenously or if brain histamine was simply derived from mast cells that have been shown to migrate into the brain under some circumstances [152] and to form synapse-like structures with neurites [155]. The other objection was based on the fact that it was difficult to visualize histamine in the brain using the histochemical methods of the nineteen-sixties and seventies. The Falck-Hillarp method of visualizing biogenic amines was used to shed light on the histology of catecholamines with great success [5, 99, 156, 157]. This method could not however detect histamine due to extensive cross-reaction with other polyamines present in brain tissue [152], thus adding to the reluctance to accept histamine as a transmitter of the central nervous system. The development of immunohistochemistry and histamine-reactive antibodies [158] made it possible to trace the histaminergic axonal pathways. Demonstrating that there was a single brain nucleus in an area of the hypothalamus, known for its importance in wakefulness, that gives rise to the histamine producing axons made it possible for histamine to gain acceptance [152].

The histaminergic neurons of the tuberomamillary nucleus exhibit a pacemaker-like firing pattern [159]. This enables sustained slow regular discharge during quiet wakefulness, which is discontinued during sleep. By this mechanism histamine is released in many areas of the brain where it can promote alertness [160]. Histaminergic fibers do not form close synapses but rather engage in diffuse volume transmission from axon varicosities [161]. The hypothalamus is particularly innervated as well as the septal nuclei, the VTA and SNpc. The olfactory bulbs, thalamus, neocortical areas, amygdala and hippocampus receive a moderate amount of innervation whereas the striatum receives a lesser degree of the projections [158]. Based on the regions, which receive histaminergic innervation, it has been suggested that histamine also has a “limbic” function in the brain.

Four histamine receptors have been described in mammals; H1-4, all of which are G-protein coupled receptors. There has however been speculations about a histamine receptor-coupled chloride conductance [162]. Even though there is a histaminergic ion channel in insects no such channel has been identified in mammals [152]. The H1 and H2 receptors are coupled to G_q and G_s proteins, respectively, and are therefore largely excitatory [163]. The H3 and H4 receptors, on the other hand, are coupled to $G_{i/o}$ proteins and are therefore largely inhibitory [164, 165]. The H1 and H2 receptors have received considerable interest both in the CNS and in the periphery. The H4 receptor was believed until a few years ago not to exist in the CNS [166] and its existence there is still controversial [167].

The histaminergic system has not been shown to be involved in the cause of any psychiatric disorder [152] but histamine metabolites are elevated in schizophrenic patients [168] and many antipsychotics and antidepressants bind histamine receptors [169]. The histamine system may not be primarily involved in schizophrenia but the fact that many drugs bind histaminergic receptors highlights the possibility that these receptors may cause secondary effects. The antipsychotic drug clozapine has agranulocytosis as its most severe side effect, limiting its clinical use. This effect has been proposed to be due to the fact that clozapine antagonizes H2 receptors expressed by myeloid progenitor cells of the bone marrow, thus interfering with differentiation [169]. The H3 receptor has been suggested to be a target for novel wakefulness-promoting, pro-cognitive, and antipsychotic drugs to be used in addition to standard pharmaceutical therapy [170, 171].

The histamine H3 receptor is potentially involved in the regulation of cognition

Because the H3 receptor is the target of novel pro-cognitive drugs it is relevant to review potential mechanisms by which it may regulate cognitive function. Similar to what is the case for the other brain amines the H3 receptor is an auto-inhibitory receptor expressed presynaptically on histaminergic fibers [164]. Interestingly, this receptor is also expressed presynaptically on fibers of other transmitter systems, making the H3 receptor a "heteroreceptor". In presynaptic boutons the H3 receptors regulates vesicle release and synaptic plasticity [161, 172]. Consistent with the fact that calcium entry is relevant to both synaptic plasticity and transmitter release is that the H3 receptor inhibits voltage-activated calcium channels via the beta/gamma subunits of the G-protein [173]. It is therefore possible to speculate that the H3 receptor-mediated control of synaptic plasticity and transmitter release is mediated through the coupling between the G-protein subunits, and the voltage-activated

calcium channels.

The H3 receptors are expressed as several alternative splice variants and some confer changes in the preference of downstream signaling pathways. A pertinent example is the shift from the cAMP pathway to the MAPK (Mitogen-Activated Protein Kinase) pathway in certain splice variants [174]. Moreover, this receptor has been demonstrated to have "constitutive" activity, i.e. substantial activity even in the absence of an agonist [175–177]. While this might not be the case for all types of downstream effects produced by the H3 receptors, it is still an interesting feature which might yield insights into ligand-receptor interaction, and by extension the development of novel ligands.

The most extensive postsynaptic expression of H3 receptors is in the olfactory bulb and large sections of the neocortex, including visual, somatosensory, auditory, motor, premotor, and prefrontal cortices. Expression is also strong in ventral and dorsal striatum, substantia nigra pars reticulata, entorhinal cortex and the amygdala. The hippocampal complex exhibits a layered profile with strong labeling in the pyramidal cell layer of CA1 and ventral CA3, subiculum and granular layer of the dentate gyrus [178]. Several nuclei associated with neuromodulators exhibit moderate the expression of H3 receptors. These include the septal nucleus, locus coeruleus, dorsal raphe and the tuberomamillary nucleus itself. The dopaminergic nuclei, i.e. the VTA as well as the SNpc express very low amounts of the receptor [178]. Based on expression patterns of H3 receptors in regions that are heavily involved in cognition, and the fact that these receptors can regulate the release of several transmitters and regulate LTP there, it is likely that the H3 receptor has a role in regulating cognitive function.

There are several findings supporting a role for histamine in cognition even though they are often convolved with wakefulness and arousal. Antihistamines administered in low doses, for example, decrease cognitive ability with no significant change in subjective sleepiness [179]. There are direct as well as indirect mechanisms by which histamine affects cognitive function. Perhaps the most important indirect mechanism is through the histaminergic regulation of the activity of the cholinergic neurons of the nucleus basalis and septum [180, 181]. As mentioned earlier, cholinergic transmission is of crucial importance for learning and memory, and on a physiological level, such transmission sustains theta oscillations of the hippocampus. There is also direct regulation of dopaminergic, serotoninergic and noradrenergic transmission by histaminergic innervation of the VTA, dorsal raphe, and locus coeruleus nuclei, as well as indirect regulation by presynaptic expression of H3 receptors on aminergic fibers.

Several direct effects of histamine on neocortical and hippocampal areas have been reported including: general depolarization by inhibition of potassium channels [182,183] and regulation of; synaptic glutamate release [184, 185], synaptic plasticity [186] and network rhythmic activity [183, 187, 188]. The histaminergic effects in the hippocampal formation are strong [183–186, 189] and have received particular interest both with regard to cellular and synaptic mechanisms as well has general investigation of learning and memory [152]. The H3 receptor has received interest as a potential target for "pro-cognitive" drugs, which is what framed and inspired the work pertaining to histamine in this thesis. To this date however it is only Pitolisant, an H3 receptor antagonist indicated for Narcolepsy that has progressed reached as far as phase II clinical trials [190].

The potential for H3 receptor ligands to modulate physiological activity patterns underlying cognitive function was explored in 2 studies, carried out in intact rats, where theta oscillations were modulated [187, 191]. It was however not possible to ascertain if the effects were directly due to H3 receptor-mediated effects in the hippocampus or if there were indirect effects involving other brain areas. Therefore questions remain about whether the H3 receptor-mediated regulation of theta oscillation in the hippocampus is local in origin or not, and whether H3 receptor activation modulates gamma oscillations as well.

Aims

AMINERGIC neurotransmition and gamma oscillations are both important for cognitive function. Accordingly, these functions are disrupted in psychiatric disorders. The larger questions that frame this thesis work are therefore; Does aminergic neurotransmission regulate gamma oscillations in the hippocampus and if so by which mechanisms? Because these questions have not been thoroughly explored before, we focused on the following proximate aims.

- Investigate whether the histamine H3 receptor regulates gamma oscillations in the hippocampus.
- Explore if there is schizophrenia related modulation of hippocampal gamma oscillations, specifically if there is crosstalk between the dopamine D4 receptor and ErbB4 receptor in regulating gamma oscillations.
- Identify which cells and which mechanism underlying the dopamine D4 receptor mediated modulation of gamma oscillations.

Methods

Choice of experimental model

THE purpose of this section of the thesis is to provide an overview of the methods used in the published articles (a detailed description of the methods is provided in each article) and to discuss technical and methodological considerations.

The choice of experimental model in the life sciences is a most important one because it involves ethical considerations. Our contention is that the studies in this thesis were justified because they investigate physiological mechanisms that are involved in mental disorders and cognitive decline. These disorders (particularly schizophrenia and Alzheimer's disease) entail enormous suffering of patients and their loved-ones. Moreover, because of demographic trends, the incidence of such diseases is estimated to increase in the future.

Aminergic regulation of neuronal synchrony has not been an extensively studied subject and therefore there are still many unknown parameters that cannot be derived from computational studies alone. In order to address our aims we therefore had to look to either *in vivo* or *in vitro* models. For reasons listed below we chose the *in vitro* model of gamma oscillations. Procedures for husbandry, handling and humane sacrifice of animals were carried out in accordance with permits and guidelines from Norra Stockholms djurförsöksetiska kommitté, Karolinska Institutet, National Institutes of Health and Texas A&M University.

The advent of the pharmacological *in vitro* model for network gamma oscillations [44] offers several advantages for addressing our aims: (1) minimized suffering for animals (as compared to in vivo recordings), (2) reduced number of sacrificed animals because tissue preparations can be shared among experimenters (3) good access to neurons so

that simultaneous extra- and intracellular recordings can be carried out, (4) direct pharmacological access, i.e. no confounding effects of bioavailability of the various used drugs, (5) stable, long lasting oscillations making it possible to discern pharmacological effects on the characteristics of the gamma oscillation, (6) no need for anesthetic agents (during recordings) that could confound results and (7) incoming fibers to the hippocampus are of course severed, offering the possibility of studying this network in isolation.

Tissue preparation and maintenance

Animals were deeply anesthetized before being sacrificed. Experiments were carried out in horizontal sections (300 microns thick, prepared with a vibratome) of the ventral hippocampi of rats of both hemispheres. Immediately after cutting, sections were transferred to a humidified, oxygenated holding chamber (interface-type) and allowed to recover for a minimum of 1 hr. All recordings were carried out in a submerged recording chamber using standard visualization and recording techniques (see papers). The slices were superfused with artificial cerebrospinal fluid (ACSF) that was continuously bubbled with 95% oxygen and 5% carbon dioxide at a rate of 4-7 ml/min to ensure enough oxygenation to sustain oscillations.

Oscillations

Gamma oscillations were induced by the application of low concentrations of kainic acid (100 nanomolar) or carbachol (2-20 micromolar). This activity develops in the slice for 3-10 minutes after application and is stable after 20 min. Recordings at this time point were used as the baseline. Intracellular recordings were carried out in conjunction with local field potential (LFP) recordings. LFPs were always recorded by placing the electrode in *stratum pyramidale* of area CA3. Drugs were added to ACSF and reached the slice by perfusion.

Gamma oscillations resulting from various induction methods share basic network mechanisms and circuitry but often respond differently to neuromodulators [192], (paper II). We believe that this fact accounts for the differing reports of effects of neuromodulators on *in vitro* gamma oscillations. There are several methods used to elicit gamma oscillations. These include pharmacological stimulation with agonists on muscarinic receptors, kainate receptors and metabotropic glutamate receptors [44, 66, 193, 194], as well as direct electrical stimulation [66]. *In vivo* optogenetic drive of parvalbumin-positive interneurons can also elicit oscillations [74]. The unifying principle for these methods of inducing gamma oscillations is the excitation of fast-spiking perisomatic-targeting GABAergic interneurons [73, 195]. Gamma oscillations can arise also spontaneously in some hippocampal slice preparations [196], but these are less stable then oscillations

induced by pharmacological means. It has been suggested that gamma oscillations *in vivo* can manifest in 4 different ways [197]: (1) non-sensory, non-task dependent, spontaneous background gamma oscillations, (2) evoked oscillations, believed to be associated with neuronal sensory processing, (3) induced gamma oscillations, believed to be associated with perceptual or cognitive object representations, (4) steady-state gamma oscillations, believed to be associated with sensory processing of rhythmical stimuli. Which one of these 4 modes is most closely matched by pharmacologically induced *in vitro* gamma oscillations is not known. It is however important bear in mind the fact that there are different types of gamma oscillations when comparing studies.

Analysis

Power spectral density plots (from 60 s long LFP recordings) were calculated from averaged Fourier-segments, power was calculated by integrating between 20 and 80 Hz. The oscillation frequency is linearly dependent on recording temperature [78] and because we record at 32°C, our power spectra have a peak at a frequency around 30 Hz. In papers I and III we tested the hypothesis that gamma oscillations are modulated by regulation of excitatory and inhibitory postsynaptic currents. These measurements were analyzed by using a template-based algorithm included in the Axograph X software package [198]. We also investigated neuronal action potential phase-synchronization. The instantaneous phase and the degree of phase modulation was calculated in different ways in paper I and III mostly owing to the opposite effects but also due to refinement of our analysis approach. In paper I a template-based algorithm for identifying field cycles was used in conjunction with an inverse sine function to identify instantaneous phase. Action potentials were then plotted in histograms according to instantaneous phase and a 3rd order polynomial function was fitted to the histogram. The 3rd order coefficient of the fitted functions correspond to the "peakedness" of the phase histogram and is therefore taken as a measure of phase-coupling [199]. Because phase-synchrony instead increased in paper III the method used in paper I became unwieldy. In paper III, Hilbert transforms were carried out on band-pass filtered (20-40 Hz) LFP recordings to find the instantaneous phases of the gamma cycles [200]. The phase-angles and the angular phase-coupling of the action potentials were calculated by vector averaging (using custom written routines in MATLAB). Each action potential had a phase angle and could therefore be described as vector with length 1. The vector average of the phases of all the action potentials recorded in one cell had a length between 0 and 1 where longer vectors correspond to higher degrees of phase-coupling. The angle of the resultant vector represents the preferred firing angle of the neurons.

Results and Discussion

Paper I

In paper I we show that the selective activation of H3 receptors can cause a significant reduction in the power of neuronal network activity in the gamma-frequency range in the hippocampus *in vitro*. This effect, elicited by the selective H3 receptor agonist R-alpha-Methylhistamine (RAMH) on kainic acid-induced gamma oscillations, is specific to the H3 receptor as the reduction is abolished by Clobenpropit, an H3 receptor antagonist.

Several cellular and synaptic mechanisms can explain a decrease in field oscillation power. Oscillatory network activity is highly dependent upon (1) concerted and balanced excitatory and inhibitory synaptic activity, (2) a basic level of depolarization to pyramidal cells and interneurons and (3) phase-synchronized action potential discharges [44, 199, 201, 202]. Disruption of any of these parameters can result in decreased gamma oscillation power. We proceeded to test 3 plausible mechanistic hypotheses that could underlie a decrease in power; (1) There may be a marked decrease in synaptic activity, (2) the level of excitation in the network could decrease, (3) there may be a decrease of the phase-synchrony of action potential discharges.

The decrease in gamma oscillation power was not due to overall decreased synaptic activity, since neither synaptic event amplitude nor frequency decreased in response to H3 receptor activation. The slow inward current elicited by kainate as well as the frequency of action potential firing in pyramidal cells were also unaffected. Instead, we found a substantial desynchronization of action potential firing in hippocampal pyramidal neurons in relation to the gamma cycle. This data supports the notion that desynchronization caused the observed reduction in power. A correlation between reduced synchronous discharge of action potentials among pyramidal neurons in CA1 and

reduced power of network oscillations has been reported previously [202]. We propose that a similar desynchronization mechanism is present in CA3, which generates rhythms and transmits them to CA1.

Because this was the first study specifically concerned with histaminergic modulation of gamma oscillations, there are still many outstanding questions. The specific mechanism underlying the H3 receptor-induced desynchronization of action potential firing in pyramidal neurons remains to be further investigated. At least two possible modes of regulating action potential phasing can be envisioned: either a direct modulation of the pyramidal neurons themselves, or an indirect effect causing changes in other cells of the network, which then affect pyramidal neurons. It is possible that H3 receptor agonists, acting directly on pyramidal neurons, reduce their ability to follow the network oscillation rhythm.

One possibility is that afterhyperpolarization (AHP) is affected in pyramidal cells, thereby affecting the phasing of action potentials. Histamine, acting through the H2 receptor, has been shown to regulate afterhyperpolarization amplitude in CA3 pyramidal neurons, thereby controlling inter-spike-intervals [152].

Another possible mode of inhibition of rhythmic network activity was demonstrated in a study on cannabinoids, where stimulation of the cannabinoid CB1 receptor reduced the power of network oscillations, possibly through presynaptic inhibition of cholecystokinin (CCK) expressing interneurons [193]. In a mechanism similar to what has been reported for H3 receptors [173], CB1 receptors are presynaptic inhibitory heteroreceptors [203], and inhibit transmitter release by inhibiting N-, P/Q-type calcium channels. Such a mechanisms would rely on H3 receptor-expressing interneurons having a diminished capability to coordinate pyramidal neuron firing in phase-locked synchrony with the ongoing gamma oscillation in the presence of RAMH. Our data only show a slight decrease in the mean amplitudes of IPSCs during RAMH treatment, suggesting that H3 receptors do not have a strong influence on general IPSC strength. However, our experiments do not differentiate between IPSCs from the various subtypes of interneurons active during gamma oscillations. One can speculate that a subpopulation of interneurons exhibits decreased transmitter release in response to H3 receptor mediated inhibition. This potential effect cannot be distinguished in our data sets because it is potentially masked by the activity of unaffected GABAergic synapses.

In a separate set of experiments we found that stimulating H3 receptors did not significantly reduce the power of carbachol-induced gamma oscillations. Another group found that H1 and H2 receptor antagonists could, respectively, increase and decrease the power of

gamma oscillations induced by acetylcholine in a hippocampal slice preparation similar to ours [204]. In addition, they present the conjecture that acetylcholine causes the release of histamine which is then tonically modulating the gamma oscillations. While, this potential mechanism does not contradict our findings, acquiring data to directly test whether this notion holds true in *in vitro* preparations is necessary to ascertain its validity.

The physiological relevance of the reduction of kainic acid-induced gamma oscillations produced by H3 receptor activation is, however, emphasized by two studies concerned with histamine modulation of theta oscillations in the hippocampus *in vivo*. In the first study, blocking the H3 receptor resulted in higher power of theta oscillations [187]. This effect could be explained by local histamine action such as a direct effect of H3 receptor on the network or by H3 receptor acting in the capacity of an autoinhibitory receptor on histaminergic fibers where H3 receptor blockade increases tonic histamine release. In addition, there could also be histaminergic effects outside the hippocampal network that have an indirect effect on the hippocampus. In this scenario, the increased level of histamine would stimulate the histamine receptors (i.e. H1, H2 and H4). These receptors would then have an increased capability of sustaining or increasing the power of theta (and possibly other) oscillations. The net result would be the same for both scenarios: block of H3 receptor, whether it exerts its effect directly or indirectly, would increase the power of theta oscillations. A second study, also concerned with theta oscillations in the hippocampus *in vivo*, demonstrated that H1 receptor blockade produces memory deficits with a concomitant decrease in theta power [191]. These deficits were ameliorated by NMDA receptor agonists but exacerbated again with the addition of an H3 receptor agonist. The results presented in paper I do not differentiate between a direct action of H3 receptors or an indirect action via H3 receptor-mediated autoinhibition with subsequent reduction of histamine release and activity of the other histamine receptors. Fibers originating in the histaminergic tuberomamillary nucleus innervate ventral CA3a and CA2 [154], moreover *in situ* hybridization shows that the H3 receptor is strongly expressed in the ventral hippocampal complex of rats [178], but the subcellular localization in this area has not yet been determined. The available histological data cannot exclude one possibility or the other at this point. The histological data does however suggest that histamine has an important role in modulating CA2/3 networks. We show that the H3 receptor can regulate hippocampal gamma oscillations and may therefore be relevant target for pharmaceutical development of pro-cognitive or antipsychotic substances.

Paper II

We systematically assayed the effects of activating the various dopamine receptors on kainic acid-induced gamma oscillations. Dopamine applied (across a wide range of concentrations) did not produce an effect in amplitude or frequency. By using a combination of antagonists and agonists with specificity for D1/5, D2/3, and D4 receptors, we revealed a selective D4 receptor-mediated increase in power of kainic-acid induced gamma oscillations. In earlier studies, the Heinemann group showed that D1/5 receptor activation produced decreases in carbachol- and kainic acid-induced gamma oscillations [192, 205]. We, in contrast, did not find that D1/5 receptor activation decreases kainic acid-induced gamma oscillation power outright. Our observations suggest instead that D1/5 receptor activity can counteract the D4 receptor-mediated increase in gamma oscillation power. Activation of the D2/3 receptors produced no result in our study but a recent study from the Heinemann group, using acetylcholine-induced oscillations, found that D3 receptors may decrease the power of gamma oscillations [206].

ErbB4 receptor-activation mediates depotentiation of hippocampal long-term synaptic potentiation [111] and increases gamma oscillation power in the hippocampus [207]. Selective D4 receptor antagonists and the antipsychotic drug Clozapine (which has more potent antagonism on D4 receptors than on D2 receptors) have been demonstrated to inhibit the acute effects of the neuropeptide neuregulin-1 and its receptor ErbB4 [111]. Consistent with these reports, we found that neuregulin-1-induced increases in gamma oscillation power are significantly reduced by a selective D4 receptor antagonist and by clozapine.

Because D4 and ErbB4 receptors seem to interact it was relevant to investigate the possibility that the receptors are coexpressed. To this end, our collaborators carried out immunohistofluorescence and *in situ* hybridization experiments, finding that ErbB4 and D4 receptors are coexpressed in parvalbumin-expressing interneurons. These findings are consistent with what others have reported in the prefrontal cortex and the hippocampus [208–210]. The parvalbumin-expressing neurons are mostly found in, or close to, *stratum pyramidale* of both CA1 and CA3. Because the parvalbumin-expressing interneurons are crucial for the generation of gamma oscillations it is plausible that receptor activation on these interneurons modulate the oscillations. Based on our data we therefore conclude that the crosstalk between dopamine and Neuregulin-1, with regard to gamma oscillations is mediated by the D4 and ErbB4 receptors on parvalbumin expressing interneurons.

An increase in power is hypothesized to lead to increased gain of neuronal signaling [211], i.e. EPSCs are more likely to trigger spikes and thus integrating and propagating information more efficiently across neural networks [15, 23]. This can lead to increased signal-to-noise ratios in case the increased gamma oscillation power is transient. In contrast, increased gamma power can lead to the opposite if it is persistent and irrelevant information propagates with high gain. An hypothesis has been put forward suggesting that with increased gamma oscillation "background power" and decreased dynamic task-related increases in response to real cognitive need, irrelevant and inconsistent stimuli are ascribed undue cognitive salience [82]. Dopamine has a prominent role in the mediating cognitive salience and aberrant cognitive salience is a prominent feature of schizophrenia [212]. It has been suggested that D4 receptors are involved in setting the salience "value" during associative learning whereas D1 receptors are involved during memory recall [213]. In the light of our findings, we speculate that hyper-activation of D4 receptors could potentially increase "background gamma" oscillation power. It is clear that D4 receptor antagonists do not remove positive symptoms but perhaps they can reduce the abnormally elevated background gamma power in schizophrenic patients.

Cross-talk, between D4 and ErbB4 receptors taken together with: (1) the fact that polymorphisms in the NRG-1 and ErbB4 genes are associated with schizophrenia-like endophenotypes [94], (2) elevated risk for schizophrenia [94], (3) that gamma oscillations are altered in patients with the disorder [82,83,88], (4) that reductions in parvalbumin-expressing interneurons are reported in postmortem brains of affected individuals [214, 215], and (5) parvalbumin-expressing interneurons are believed to be critical for working memory and other cognitive functions, point to the conjecture that an important nexus exists, where parvalbumin expressing neurons, genes and network activity associated with psychiatric disorders intersect.

Paper III

In this study we show that the antipsychotic drug Clozapine can block the D4 receptor-mediated increase in gamma oscillations, analogous to the pharmacological effect of the specific D4 receptor antagonist L745,870, thereby confirming the findings in paper II. Following the findings in paper II, we set out to investigate how D4 receptor activation can modulate gamma oscillations on the cellular level.

Postsynaptic potentials in pyramidal cells contribute substantially to the local field potential (LFP) deflections, making up the oscillation [44, 71]. For this reason, we explored the possibility of D4 receptor-mediated modulation of EPSCs or IPSCs in pyramidal cells. We did not find any systematic difference in amplitudes or coherence of

EPSCs in pyramidal cells. IPSCs and pyramidal cell action potential discharge carry more weight in influencing the LFP oscillations than the EPSCs [71]. We therefore reasoned that a potential mechanism by which gamma oscillation power can be modulated may entail changes in pyramidal cell spike-phase coupling (also known as depth of modulation) or the coherence and amplitudes of IPSCs. In contrast to what we found in paper I, there was no change in pyramidal cell spike-phase coupling. Nor were there any changes in the amplitudes of IPSCs in pyramidal cells. Instead, the coherence between IPSCs and LFP oscillations increased. In previous studies we and others found that phase-desynchronization of pyramidal cell discharge in the hippocampus during gamma oscillations decrease their power (paper I), [199, 202]. Because we found increased gamma oscillation power in this case, one possible mechanism is that the increased power could be caused by increased pyramidal cell firing synchrony. The data suggested otherwise (i.e. spike-phase coupling and coherence of pyramidal cell action potential discharge remained unchanged) and we were led to the conclusion that the increased power was not driven by increased pyramidal cell synchrony.

The coherence of the IPSCs, on the other hand, was increased. We reasoned that it is possible that there may be a change in the spiking patterns of one or several of the groups of interneurons. There are several different classifications of interneurons based on their histological, physiological and genetic traits. We chose to broadly divide them into 2 classes based on their physiological properties; fast-spiking (FS) and non-fast spiking (nFS) interneurons. Our recordings showed that the spike-phase coupling increased in FS, whereas it did not change in nFS. Increases in discharge rates as well as increases in spike-phase coupling have been identified as mechanisms underlying increases in gamma oscillation power *in vivo* [216]. None of the cell-types in this study changed the overall firing rate as a result of D4 receptor activation. In the light of our data, and because fast-spiking interneurons are crucial for the generation of gamma oscillations, we concluded that the increased synchrony among fast-spiking interneurons was the underlying cause for the observed increase in gamma oscillation power.

We then went on to consider what mechanisms may underlie the increase in FS synchrony. We reasoned that such a mechanism could either be intrinsic to these interneurons or, alternatively, may involve their synaptic function. In order to investigate the potential intrinsic mechanisms of D4 receptor modulation we carried out voltage-step recordings. This method can reveal changes in kinetics and conductance of voltage-gated ion-channels such as Kv7/KCNQ, which in turn can alter neuronal synchrony [199, 217]. Activation of the D4 receptor did indeed decrease an outward current (or increased

an inward current), but only at very depolarized voltages. The difference at these voltages, which under physiological settings would only be reached during action potential discharge, did not carry over in to producing any differences in action potential half width or afterhyperpolarization amplitude. We therefore concluded that this decrease in outward current at very depolarized potentials was not a mechanism likely to account for increasing the spike-phase coupling of FS.

As we did not find a satisfactory explanation involving voltage-gated currents, we turned to investigate synaptic mechanisms. There is a myriad of potential direct and indirect ionotropic and metabotropic receptor mediated mechanisms. We chose to focus on a few ionotropic receptors the D4 receptor has been shown to modulate, the $GABA_A$ [150], the AMPA [151], and the NMDA receptors [112, 148]. D4 receptor mediated modulation of $GABA_A$ receptors is likely not present in this study because changes in conductance of $GABA_A$ receptors in fast-spiking interneurons produce frequency shifts in the LFP oscillations [218] and shifts in the phase angle of rhythmical firing [219]. As we observed neither a local field potential oscillation frequency shift nor shifts in fast-spiking, non-fast spiking or pyramidal cell preferred firing angle, our data do not support a mechanism involving regulation of $GABA_A$ receptor currents in fast spiking interneurons.

We next considered modulation of excitatory synaptic transmission onto FS interneurons as this is a potential mechanism subject to dysregulation in schizophrenia [220]. Reports from the prefrontal cortex have indicated that the selective D4 receptor agonist PD168077 decreases surface expression of AMPA receptors in parvalbumin-expressing interneurons [151]. We could not detect any effects on largely AMPA receptor-mediated EPSC amplitudes, half-widths or number of events in our experiments. Therefore we went on to examine the role of the NMDA receptor, which is believed to be implicated in the cognitive deficits in schizophrenia and is central to the glutamate hypothesis of schizophrenia. NMDA receptor antagonists (in particular ketamine and phencyclidine) elicit psychotic symptoms and cognitive deficits in humans [220]. D4 receptor activation has been reported to influence NMDA receptor-mediated currents, synaptic plasticity and novel object recognition [112, 142] but it has not previously been reported that D4 and NMDA receptors interact to influence gamma oscillations. While, it has been suggested that membrane expression of NMDA receptors on pyramidal cells in the prefrontal cortex can be regulated by D4 receptor [148], we instead wanted to highlight the role of NMDA receptors on hippocampal FS as these neurons altered their firing pattern in response to D4 receptor activation. To test the involvement of NMDA receptors in the D4

receptor-mediated increase in power, we applied the NMDA receptor antagonist AP5. This compound did not change gamma oscillation power on its own but it completely abolished the increase in oscillation power produced by D4 receptor activation. Bath application of AP5 is not specific with regard to FS. Interneurons are, however more sensitive than pyramidal cells to NMDA receptor antagonists because they express higher levels of the receptor [221–223]. Consistent with this finding, injections of NMDA receptor antagonists in animals [223] and selective genetic ablation of NMDA receptors in parvalbumin expressing interneurons [75, 76] produce gamma and theta band disturbances as well as deficits in cognition and perception. Removing NMDA receptor function, by pharmacological or genetic means, in parvalbumin-expressing interneurons is therefore sufficient to exert a modifying influence on gamma and theta oscillations.

Because AP5 application did not decrease the kainic acid-induced gamma oscillation power, but merely removed the D4 receptor mediated increase, we conclude that NMDA receptors are not needed for a basic level of gamma power when excitation in FS is generated by other means such as activation with kainic acid. This has also been shown previously with carbachol-induced oscillations [44]. Increasing the power beyond the basic level may however require phasic excitatory feedback from pyramidal cells onto FS mediated by NMDA receptors.

Future studies will have to be carried out in order to test the hypothesis that it is D4 receptor activation that increases NMDA receptor-mediated currents in FS. This could potentially explain the increased spike-phase coupling and coherence observed in FS. Blocking a substantial amount of these receptors by adding AP5 would, in line with what we observed, abolish the PD168077 effect. The effects of NMDA receptor blockade or ablation is complex however. *In vivo* studies show that blocking or ablating the NMDA receptor produces an increase in gamma and decrease in theta power in itself [75, 76, 223]. During cognitively demanding tasks, intact animals and healthy humans respond with a dynamic increase of gamma power over "background" levels. In patients with schizophrenia however, the background level of gamma is elevated whereas the task-related increase in gamma power is attenuated (relative to "background" levels) [82]. This effect is also present in animals with blocked or ablated NMDA receptors [75, 76, 223].

A recent paper showed that when FS in animals lacking NMDA receptors are selectively driven by optogenetic stimulation, gamma oscillations are not generated to the same extent as in normal animals [76]. A possible explanation for this is that NMDA receptors are needed to provide local excitatory feedback on to these interneurons

once they establish a phase modulated discharge pattern among the pyramidal cells. Without the NMDA receptors present, the loss of excitatory feedback means that the local network fails to "resonate" at gamma frequencies to the same extent as an intact circuit. One interesting question is therefore: if NMDA receptors in parvalbumin positive-interneurons are important for gamma oscillation "resonance" why is there an increase in background gamma power in animals where this receptor has been ablated? As *local* neocortical and hippocampal circuits were less able to "resonate" at gamma frequencies it has been hypothesized that the increase in gamma power is driven by thalamocortical [76] and possibly septohippocampal excitation [224] respectively. In the hippocampus there was a decrease in theta power, but the activity that remained in this frequency range was dependent upon muscarinergic receptors, thus further implicating the medial septum [75].

In contrast to what has been reported in *in vivo* experiments [75, 76, 223] the experiments from paper III showed that applying AP5 did not increase the power of kainic acid-induced gamma oscillations in *in vitro* hippocampal preparations, replicating *in vitro* results found by others [201, 225]. This discrepancy between *in vivo* and *in vitro* experiments does at least not rule out the possibility of thalamocortical and septohippocampal input driving aberrant background gamma oscillations.

Taken together, we show that activating the D4 receptors produces increased gamma power that is driven by an increased phase-synchrony of FS, while pyramidal cells and nFS remain unchanged in their spiking pattern. The AMPA receptor-mediated EPSCs were unaffected by D4 receptor activation in FS. This was also the case for voltage-activated currents in these cells (except at voltages well above the threshold for action potential discharge). We found however, that the D4 receptor-mediated increase in power is NMDA receptor-dependent as this increase could be blocked by the NMDA receptor antagonist AP5. The fact that D4 receptor antagonists were ineffective as antipsychotic drugs in clinical trials [138–140], leads to a reinforced conclusion that the main antipsychotic effect is carried by D2 receptors. Our results, on the other hand, show that it is possible to modulate gamma oscillations *in vitro* by regulating D4 receptor activity, potentially restoring the physiological information processing of neural networks. This activity is likely more relevant for the cognitive deficits than it is for the positive symptoms in schizophrenia. It might therefore be of interest to investigate D4 receptor ligands as adjuvant therapy to standard D2 receptor antagonist antipsychotics in future clinical studies.

Closing remarks

Because cognitive function is closely associated with gamma oscillations and cognitive disturbances are core features of schizophrenia with the most impact on patient outcomes, it is important to explore new avenues for addressing cognitive deficits. The aminergic systems of the brain are intimately involved in regulating cognitive function and are hence important targets. In our studies we have shown that it is possible to bi-directionally regulate the power of hippocampal gamma oscillations by activating histaminergic and dopaminergic receptors. Interestingly, the H3 and D4 receptors are both $G_{i/o}$ coupled receptors yet they exert opposing effects on gamma power. This can perhaps be explained by differential expression of receptors on pyramidal cells and parvalbumin-expressing interneurons respectively. We did not observe any changes in the amplitude of excitatory or inhibitory postsynaptic currents nor the rate of action potential firing. Rather, it was the neuronal phase-synchronization that changed as a result of activating H3 and D4 receptors. Aminergic regulation of neuronal synchrony offers the possibility of regulating the gain of neuronal communication without changing entrant information to the neuronal network. For this reason, we believe that ligands on these receptors can be developed for the purpose restoring physiological gamma oscillations in patients with psychiatric and neurodegenerative disorders.

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