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GABAergic mechanisms of hippocampal hyperactivity in schizophrenia

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Abstract

Schizophrenia is associated with abnormalities of hippocampal structure and function. Neuroimaging studies have shown that the hippocampus is hyperactive in schizophrenia. Here we explore GABAergic mechanisms of this hippocampal hyperactivity.

The initial evidence for GABAergic abnormalities of the hippocampus in schizophrenia came from post-mortem studies of interneuron number, protein expression, and gene expression. These studies revealed marked decreases in gene and protein expression of somatostatin-positive and parvalbumin-positive interneurons, and indicated reduced interneuron numbers. Animal studies of decreased parvalbumin and NMDA-receptor function have shown that selective abnormalities of hippocampal interneurons mimic some of the cognitive deficits and clinical features of schizophrenia.

The post-mortem and animal studies are consistent with the neuroimaging finding of increased hippocampal activity in schizophrenia, which can explain some of the psychotic symptoms and cognitive deficits. Taken together, these findings may guide the development of biomarkers and the development of new treatments for psychosis.

The hippocampus is abnormal in schizophrenia (Benes, 1999; Heckers and Konradi, 2010; Nelson et al., 1998; Tamminga et al., 2010; Wright et al., 2000). Two prominent features of schizophrenia, reality distortion (delusions and hallucinations) and cognitive deficits have been linked to hippocampal dysfunction and several neural models of schizophrenia posit abnormalities of the hippocampus (Heckers and Konradi, 2010; Tamminga et al., 2010).

In this review we will focus on the hypothesis that hippocampal hyperactivity is a core feature of schizophrenia. In particular, we will highlight GABAergic mechanisms of hippocampal hyperactivity in schizophrenia. We will review the evolution of the hippocampal hyperactivity model of schizophrenia and clarify the term hippocampal

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Conflict of Interest

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hyperactivity. We will summarize the evidence generated so far in support of GABAergic mechanisms and propose a developmental model of GABAergic mechanisms, giving rise to hippocampal dysfunction in schizophrenia.

Evolution of the hippocampal hyperactivity model

Even before any studies of the hippocampus, several authors proposed models of hippocampal hyperactivity in schizophrenia (Krieckhaus et al., 1992; Venables, 1992). These authors hypothesized that deficits seen in patients with schizophrenia (e.g., latent inhibition and negative priming) are caused by hippocampal hyperactivity, but did not provide any experimental data. This changed with Peter Liddle's 1992 study of patterns of cerebral blood flow in schizophrenia and Francine Benes' 1998 study of a selective decrease in the number of hippocampal interneurons in schizophrenia.

Liddle et al. studied 30 patients with schizophrenia, who were classified into three syndromes based on a stable pattern of psychopathology: 1) psychomotor poverty (i.e., mainly negative symptoms), 2) disorganization and 3) reality distortion (i.e., mainly positive symptoms). The authors reported significant positive correlations between reality distortion and rCBF in the left temporal lobe, especially the parahippocampal region (Liddle et al., 1992).

A complementary analysis of the same data set (Friston et al, 1992) provided a more detailed discussion of temporal lobe hyperactivity in schizophrenia: "An obvious inference is that severe schizophrenia is associated with increased transynaptic activity (inhibitory or excitatory) mediating the transformation of neuronal firing patterns. In other words, a reduction in the efficiency of these transformations. The anatomical substrate of this positive physiological correlate may include atrophic changes, but the nature of the presumed dysplasia is such that it results in higher rCBF." This introduces several components of current models of hippocampal hyperactivity in schizophrenia: synaptic dysfunction, abnormal neuronal firing pattern, efficiency of neurotransmission, and atrophy of the hippocampus.

Benes et al. reported that the density of pyramidal cells (glutamatergic neurons) is normal in schizophrenia, but that nonpyramidal (GABAergic) neurons are selectively reduced in sector CA2 (Benes et al., 1998). Benes and Berretta conjectured "that decreased GABAergic transmission in specific cortical areas could result in rearrangement, and possibly enlargement, of sensory, memory and 'cognitive' fields and thereby lead to overinclusive, disorganized thought processes." (Benes and Berretta, 2001). This introduces several other aspects of current hippocampal hyperactivity models: decreased GABAergic neurotransmission, rearrangement of cognitive fields, and, as a result, abnormal thought processes.

In addition to these two important studies, several other observations support a hippocampal hyperactivity model of schizophrenia. First, schizophrenia is associated with impaired habituation, i.e. an inability to modulate responses after repeated presentations of sensory stimuli (Rankin et al., 2009). Freedman and colleagues have proposed that alpha-7 nicotinic receptors on hippocampal interneurons are the primary site of pathology underlying the

impaired filtering of sensory information in schizophrenia (Freedman et al., 2000). Support for this model from neuroimaging data was recently reviewed by Tregellas (Tregellas, 2014). For example, patients with schizophrenia demonstrate significantly greater activation of the hippocampus while passively viewing facial expressions (Holt et al., 2006) and do not show the normal pattern of habituation to the repeated presentation of fearful faces (Holt et al., 2005). This failure of habituation is correlated with the degree of memory deficits in schizophrenia (Williams et al., 2013).

Second, specific memory deficits in schizophrenia have been linked to abnormal hippocampal function. The initial study showed an increased activity of the hippocampus and decreased recruitment during the performance of a memory retrieval task (Heckers et al., 1998). This finding was confirmed and extended by several studies, which revealed that hippocampus-dependent memory is more impaired than memory that does not rely on the hippocampus (Achim et al., 2007; Ongur et al., 2006; Weiss et al., 2003). More recently, Tregellas provided evidence that intrinsic hippocampal activity at rest is related to cognitive dysfunction in schizophrenia (Tregellas et al., 2014).

Third, the dopamine hypothesis of schizophrenia has been linked to hippocampal hyperactivity. Elevated regional cerebral blood flow in the hippocampus of schizophrenia patients is normalized by D2-antagonists (Medoff et al., 2001). Dopamine facilitates hippocampus-specific cognitive tasks at higher levels, but is detrimental at levels above the optimal range (Chowdhury et al., 2012; Rocchetti et al., 2014). One proposed mechanism is the inhibition of perforant path input to CA1 by dopamine, which is reversed with antipsychotic drugs (Lisman and Otmakhova, 2001#12809). In addition, a hyperactive dopamine system increases hippocampal activity and increased hippocampal activity triggers a hyperactive dopamine system (via reciprocal connections between hippocampal formation and midbrain dopamine neurons) (Lisman et al., 2008). For example, in the methylazoxymethanol acetate (MAM) rodent model of schizophrenia, which disrupts prenatal hippocampal development, a primary disturbance in the hippocampus increases the spontaneous firing rate of dopaminergic neurons in the ventral tegmental area (Lodge and Grace, 2007). In this model, antipsychotic drugs reduced the number of spontaneously active dopamine neurons (Valenti et al., 2011) and transplanted GABAergic neuronal precursors reversed the physiological and behavioral deficits (Perez and Lodge, 2013).

Taken together, there is now compelling evidence that hippocampal hyperactivity is a possible mechanism for psychosis. Several models have been proposed, which focus on hippocampal-cortical interactions (Heckers, 2001) and the distinct roles of subfields CA1 (Small et al., 2011), CA2/3 (Benes, 1999), and hilus/dentate gyrus (Tamminga et al., 2010).

Excitation-inhibition balance in the hippocampus

The hyperactivity model of schizophrenia states that the excitation-inhibition (E/I) balance is abnormal in psychosis (Uhlhaas, 2013). This has been proposed for several brain areas, including the hippocampus. Here we will briefly review the E/I balance in the human hippocampus.

Excitation in the hippocampus

The vast majority of hippocampal neurons (approximately 90%) are glutamatergic pyramidal cells (also referred to as principal cells), (Freund and Buzsaki, 1996; Olbrich and Braak, 1985). This is markedly different from the cerebral cortex, where the numbers of pyramidal and nonpyramidal cells are more balanced (Mouton, 2014). This E/I imbalance makes the hippocampus more vulnerable to focal excitation and seizures. Pyramidal cells project either within hippocampal subfields (intrinsic circuitry) or via long-range projections to several target areas (hippocampal efferents). These glutamatergic neurons have a high baseline firing rate and are synchronized into oscillatory patterns by a plethora of interneuron subtypes (Klausberger and Somogyi, 2008). Synaptic input to the soma, the axon and dendrites of pyramidal neurons is arranged according to the origin and characteristics of the presynaptic source. Distal dendrites receive excitatory input predominantly from distant brain areas, whereas basal and proximal dendrites receive excitatory input from local sources (Spruston, 2008). Inhibitory interneurons synapse in the perisomatic area, the axons and dendrites, with different interneuron subtypes targeting specific subcellular components (Freund and Buzsaki, 1996; McBain and Fisahn, 2001).

Inhibition in the hippocampus

Only 10% of hippocampal neurons are GABAergic, non-pyramidal cells, which form intrinsic connections. Despite the small proportion, these interneurons exert ultimate control by synchronizing pyramidal cell populations and regulating information flow through the hippocampus, achieved via elaborate synaptic networks (Freund, 2003). Synchrony in neuronal networks is the foundation of higher brain function (Varela et al., 2001). Interneurons vary greatly in shape, dendritic arborization and axonal projections, giving rise to population subtypes characterized by morphological, neurochemical and electrophysiological properties (McBain and Fisahn, 2001). These population subtypes differ further in their functional impact on the principal cells (Freund and Buzsaki, 1996). Here we will focus on two of the largest population subtypes of hippocampal interneurons, characterized by the expression of the neuromodulator somatostatin, or the Ca^{2+} binding protein parvalbumin (Figure 1).

Somatostatin-positive interneurons constitute about a third of all hippocampal interneurons and regulate the efficacy and plasticity of excitatory inputs to hippocampal pyramidal cells (Freund and Buzsaki, 1996; Viollet et al., 2008). Somatostatin neurons play an important role in seizure control, and perturbations of the inhibitory role of somatostatin-positive neurons can lead to abnormal pyramidal cell firing (Tallent and Qiu, 2008). In the human hippocampus, somatostatin-positive neurons are dispersed throughout the pyramidal cell layer, while most of their axons terminate in the molecular cell layer on dendrites of pyramidal neurons (Figure 1), (Konradi et al., 2011a; Konradi et al., 2011b).

Parvalbumin-positive interneurons represent about 20% of all GABAergic neurons in the hippocampus (Freund and Buzsaki, 1996). They are crucial for organized temporal encoding and retrieval of information, by synchronizing the firing pattern of pyramidal cells in the 30–100 Hz range (i.e. gamma oscillations) (Bartos et al., 2007; Lewis et al., 2005). Gamma

oscillations, mediated by parvalbumin-expressing interneurons, play a central role in higher brain function (Bartos et al., 2007; Varela et al., 2001).

There are several well-known examples of E/I imbalance in the human hippocampus. Most notably, seizure disorders that originate in the hippocampus are caused by an unregulated firing of principal cells (Fritschy, 2008). In support of a role of E/I imbalance in the hippocampus, individuals with temporal lobe epilepsy have a higher incidence of psychotic symptoms than patients with generalized epilepsy (Roberts et al., 1990; Stevens, 1988). Anticonvulsants strengthen inhibition (e.g., i.v. administration of benzodiazepines in status epilepticus) or weaken excitation. More recently, increased activity of the hippocampus has also been shown in animal models of Alzheimer's Disease (AD) and in AD patients, and this hippocampal hyperactivity can explain some of the cognitive deficits and neuropsychiatric symptoms (Bakker et al., 2012; Verret et al., 2012; Wragg and Jeste, 1989).

Abnormal hippocampal activity in schizophrenia

Studies of regional cerebral glucose metabolic rates (rCMRglc), regional cerebral blood flow (rCBF) and blood oxygen level-dependent (BOLD) signal demonstrate abnormal hippocampal activity in schizophrenia (Buchsbaum et al., 1992; Nordahl et al., 1996; Tamminga et al., 1992) (Friston et al., 1992; Kawasaki et al., 1996; Kawasaki et al., 1992; Lahti et al., 2003; Liddle et al., 1992; Malaspina et al., 2004; Medoff et al., 2001). Changes of hippocampal metabolism and blood flow are associated with more severe psychopathology (Friston et al., 1992), especially positive symptoms (Gur et al., 1995; Liddle et al., 1992), such as auditory hallucinations (Dierks et al., 1999; Silbersweig et al., 1995). Intriguingly, the abnormally increased hippocampal blood flow in patients with schizophrenia is partially normalized by treatment with dopamine D2 antagonists (Lahti et al., 2003; Malaspina et al., 2004; Medoff et al., 2001).

These earlier studies of hippocampal glucose metabolism and cerebral blood flow in schizophrenia have been complemented by three recent studies of cerebral blood volume (CBV), (Schobel et al., 2013; Schobel et al., 2009; Talati et al., 2014). CBV measurements using fMRI provide sub-millimeter spatial resolution at the level of hippocampal subfields (Small et al., 2011). The two studies by Schobel et al. revealed a striking pattern in patients with prodromal and chronic schizophrenia: CBV was selectively increased in hippocampal sector CA1, which was associated with CBV increases in the orbitofrontal cortex and CBV decreases in the dorsolateral prefrontal cortex (Schobel et al., 2013; Schobel et al., 2009). The increased CBV in CA1 was recently confirmed in a cohort of chronic schizophrenia patients (Talati et al., 2014). These studies of hippocampal blood flow and blood volume support the hypothesis of abnormally elevated hippocampal activity in schizophrenia (Lisman et al., 2008; Small et al., 2011).

Hippocampal function in schizophrenia is abnormal during the performance of cognitive tasks (Hall et al., 2009; Heckers et al., 1999; Heckers et al., 1998; Jessen et al., 2003; Leavitt and Goldberg, 2009; Ongur et al., 2006; Ragland et al., 2001; Weiss et al., 2003; Weiss et al., 2004). During memory retrieval, patients with schizophrenia rely less on the recruitment of the hippocampus and show more widespread activation of the prefrontal cortex (Weiss et

al., 2003). Schizophrenia patients are especially impaired on relational memory tasks that depend on the hippocampus (Ongur et al., 2006).

While cognitive task studies have revealed impaired hippocampal recruitment in the context of increased baseline activity, several studies have provided additional evidence pointing to increased hippocampal activity in schizophrenia. In normal control probands, the hippocampal BOLD signal decreases over time when passively viewing visual stimuli. This type of hippocampal habituation is not seen in schizophrenia (Holt et al., 2006; Holt et al., 2005) and is associated with impaired memory function (Williams et al., 2013). These studies of impaired hippocampal habituation in schizophrenia have been complemented by a study of intrinsic hippocampal connectivity at rest, which also explained some of the cognitive impairments seen in schizophrenia (Tregellas et al., 2014).

Several studies have used magnetic resonance spectroscopy to measure GABA and glutamate in the hippocampus of patients with schizophrenia. Of particular interest is a recent study that linked increased hippocampal glutamate to subsequent hippocampal volume deficits in schizophrenia (Kraguljac et al., 2013).

The imaging studies reviewed here cannot reveal the cellular and molecular substrate of hippocampal hyperactivity, but this can be addressed with post-mortem and animal studies.

Reduced number of interneuron populations

While the total number of hippocampal neurons is normal in schizophrenia (Heckers et al., 1991; Konradi et al., 2011a; Schmitt et al., 2009; Walker et al., 2002), several studies have revealed selective abnormalities of interneurons. Benes et al. provided evidence for a decreased density of non-pyramidal cells in the hippocampus in schizophrenia and psychotic bipolar disorder (Benes et al., 1998). A subsequent study in these patient populations revealed decreased mRNA levels of glutamic acid decarboxylase (GAD), a marker specific for GABA synthesizing neurons (Heckers et al., 2002).

More recently, several studies have provided compelling evidence for abnormalities in subpopulations of hippocampal interneurons. Interneurons, though small in number, govern hippocampal function: they exert a dynamic, spatio-temporal control of hippocampal cell firing and are crucial for normal cognition and behavior (Somogyi and Klausberger, 2005). In particular, fast-spiking parvalbumin-expressing interneurons generate gamma oscillations which are crucial for higher brain function (Bartos et al., 2007). Neural oscillations are essential for the establishment of precise temporal relationships between neuronal responses and abnormalities in GABAergic interneurons have been proposed as the anatomical correlate for abnormal neural oscillations in schizophrenia (Uhlhaas and Singer, 2010). An initial study reported a decreased density of parvalbumin-positive neurons in all hippocampal regions (Zhang and Reynolds, 2000). This finding was independently confirmed in another study which revealed a reduction in the total number of somatostatin-positive interneurons as well as in the level of somatostatin and parvalbumin mRNA (Konradi et al., 2011a).

While the decrease in specific interneuron populations observed in post-mortem studies fits well with the neuroimaging evidence of hippocampal hyperactivity, animal models can further examine the relationship between interneurons and hippocampal hyperactivity, and elucidate the functional basis of the readouts in imaging.

Animal models of hippocampal hyperactivity

Several animal studies linked an impairment of parvalbumin-positive interneurons to abnormal hippocampal activity and schizophrenia-like behavior. Inhibition of NMDA-receptors in the hippocampus (especially in sector CA 1) decreases activity of parvalbumin-positive interneurons, which in turn leads to a disinhibition of hippocampal pyramidal cells (Behrens et al., 2007; Bickel and Javitt, 2009; Greene, 2001; Kinney et al., 2006; Lisman et al., 2008). Furthermore, administration of methylazoxymethanol (MAM) disrupts DNA synthesis in dividing cells, and when administered on gestational day 17 targets parvalbumin-containing interneurons especially in the ventral hippocampus, leading to diminished oscillatory activity (Lodge et al., 2009; Lodge and Grace, 2009). Two recent studies tested the hypothesis that the hippocampal hyperactivity seen in CBV and BOLD signal studies of schizophrenia patients (see above) are caused by abnormalities in glutamatergic or GABAergic neurotransmission. Schobel et al showed that ketamine administration leads to increased hippocampal activity as measured by gadolinium-enhanced cerebral blood volume (CBV) mapping (Schobel et al., 2013). Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, induces psychosis. It preferentially blocks NMDA receptors on GABA interneurons, which leads to a disinhibition of glutamate neurons, glutamate release and increased neuronal activity (Stone et al., 2012).

Gilani et al showed that modulation of parvalbumin-positive interneurons lead to deficits in synaptic inhibition, increased in-vivo spike activity of projection neurons and increased in-vivo basal metabolic activity (as assessed with fMRI) (Gilani et al., 2014). Even more intriguing, transplantation of cells from the embryonic ganglionic eminence (the major origin of cerebral cortical interneurons) reversed this phenotype (Perez and Lodge, 2013). These recent studies raise the question when hippocampal hyperactivity develops in psychosis.

Hippocampal hyperactivity develops in stages

Schobel et al. pioneered the longitudinal study of hippocampal activity in schizophrenia (Schobel et al., 2013). They followed subjects at risk for schizophrenia for 2 years and measured changes in CBV and hippocampal structure. They reported that subjects with higher CA1 CBV values showed greater hippocampal volume reduction after 2 years (Schobel et al., 2013). We propose that hippocampal hyperactivity in schizophrenia develops in stages.

Stage 1: Baseline risk

Several static and dynamic risk factors make subjects more vulnerable to hippocampal hyperactivity later in life (e.g., hypoxia, stress, trauma). Early stress perturbs the development of GABA neurons, which migrate over extensive distances to reach their final

location in the hippocampus. This makes them more vulnerable than interneurons in other cortical regions (Tricoire et al., 2011). Several genotypes and clinical phenotypes have been associated with a greater risk for psychosis, which include a hyperactive hippocampus in subjects at risk for psychosis.

Stage 2: Early stage of psychosis

There is growing evidence that hippocampal dysfunction (hyperactivity and smaller volume) is present in the early stage of psychosis. However, not all psychotic patients progress to a chronic psychotic disorder and some will convert to an affective disorder (Bromet et al., 2011; Salvatore et al., 2008). While it is unclear how hippocampal dysfunction can differentiate between these various trajectories, hippocampal hyperactivity is related to cognitive dysfunction (Tregellas et al., 2014; Williams et al., 2013) and reality distortion (Schobel et al., 2013).

Stage 3: Chronic psychosis

There is emerging evidence that the degree of hippocampal hyperactivity (Schobel et al., 2013) or the amount of glutamatergic dysfunction (Kraguljac et al., 2013) predict the severity of hippocampal volume loss over time in patients with schizophrenia. This provides the basis for a developmental model of hippocampal dysfunction and may offer the opportunity for a biomarker (Tregellas, 2014).

Accounting for heterogeneity

Brain changes, even robust findings such as smaller hippocampal volume, are not diagnostic for schizophrenia (Heckers et al., 2013). Several scenarios can account for this heterogeneity and need to be considered as we test the model of hippocampal hyperactivity in psychosis.

Patients who carry a significant burden of risk for the development of an abnormal hippocampus might show cognitive deficits and smaller hippocampal volume already at baseline and in the at-risk state. This includes patients with elevated genetic (e.g., DISC-1, VCFS) or environmental (hypoxia, stress) risks for a smaller hippocampus (Heckers et al., 2013). Patients with smaller hippocampal volumes in the at-risk state might show more pronounced cognitive impairment before the onset of psychosis.

Environmental risk factors may accelerate the progression of hippocampal pathology in psychotic disorders. In particular, the early and heavy use of cannabis alters hippocampal structure (Cousijn et al., 2012). Patients with such environmental risk factors might show more rapid changes in hippocampal activity and volume.

Finally, pharmacological as well as non-pharmacological treatment can alter the excitation-inhibition balance of the hippocampus and may lead to changes in hippocampal function and structure. There are compelling examples for such effects, including antipsychotic medication (Medoff et al., 2001; Schobel et al., 2013), exercise (Pajonk et al., 2010) and psychotherapy (Eack et al., 2010).

Implications for treatment

Treating the hyperactive hippocampus is a possible intervention strategy in the early stages of psychosis. This approach shows great promise in the early stages of Alzheimer's Disease. In animals that overexpress human amyloid precursor protein, the hippocampus shows spontaneous epileptiform discharges, primarily during reduced gamma oscillatory activity, which was linked to parvalbumin cell dysfunction (Verret et al., 2012). The anticonvulsant levetiracetam suppressed the abnormal spiking activity of the hippocampus and improved memory performance (Sanchez et al., 2012). In human studies, levetiracetam was able to normalize hippocampal hyperactivity (measured via the BOLD signal) and improved cognition in subjects with mild cognitive impairment (Bakker et al., 2012). These translational and treatment studies provide compelling evidence that hippocampal hyperactivity can be a treatment target for schizophrenia as well.

Summary

We propose that the neuroimaging (BOLD, CBV, and rCBF) finding of hippocampal hyperactivity in schizophrenia is due to cellular and molecular changes of hippocampal interneurons, primarily somatostatin-positive and parvalbumin-positive interneurons. We do not dispute the important role of other mechanisms (e.g., NMDA-receptor hypofunction, alpha7 nicotinergic receptor dysfunction), but for the purpose of this review we have focused on GABAergic mechanisms. We suggest that hippocampal hyperactivity in schizophrenia predates a) the onset of cognitive deficits and psychosis and b) the full course of hippocampal volume reduction seen in chronic patients. This may guide the development of biomarkers in patient populations and the development of new treatments for psychosis.

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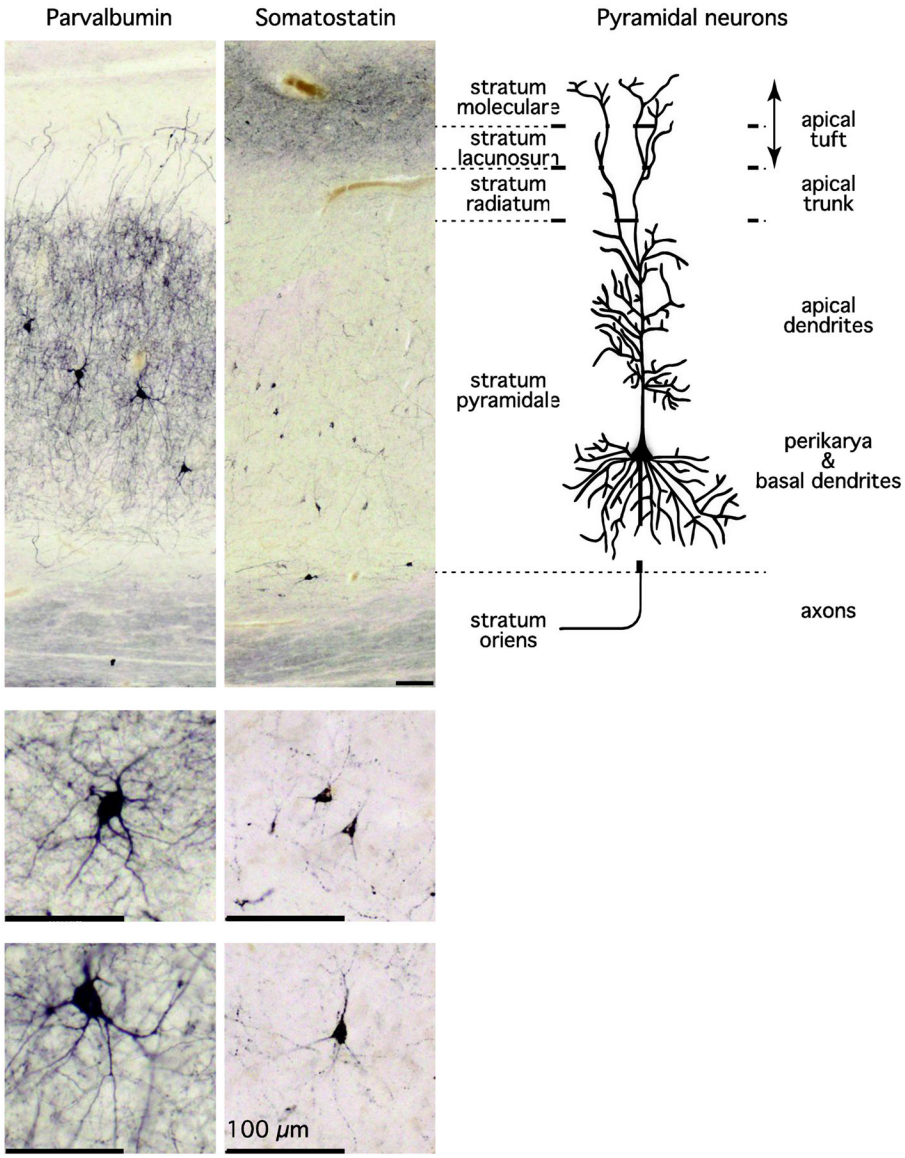

Figure 1. Parvalbumin-positive and Somatostatin-positive neurons in the human hippocampus

The photomicrographs show the cell bodies, axon and dendrites of parvalbumin-positive (left column) and somatostatin-positive (middle column) neurons in subfield CA1 of the human hippocampus, next to a schematic depiction of the position of subcellular components of pyramidal cells (right column; modified from (Spruston, 2008)). Cell somata of both interneuron populations are dispersed throughout the pyramidal cell layer. Parvalbumin-positive neurons have large somata and a high density of neurites throughout the pyramidal cell layer. A lesser density of neurites is seen in the stratum radiatum, with increasing density toward the stratum lacunosum. In contrast, somatostatin-positive neurons have smaller somata. In CA1, a group of these neurons is aligned at the border to the stratum oriens. Faint somatostatin-positive projections are seen in the pyramidal cell layer, but the highest density of neurites is seen in stratum moleculare. All scale bars = 100 μm.

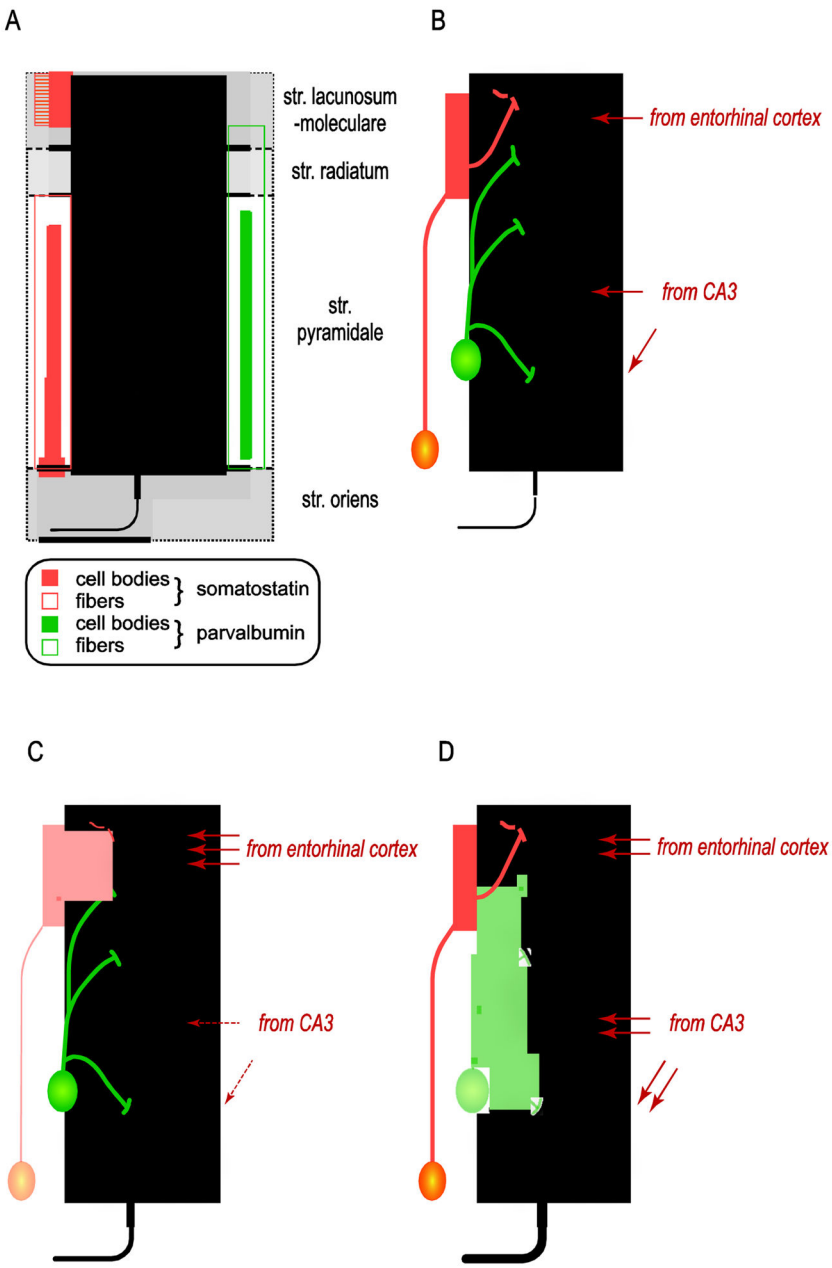

Figure 2. Altered excitation/Inhibition balance in the human hippocampus

Panel A. The majority of neurons in the human hippocampus are large, excitatory (glutamatergic) pyramidal cells. Pyramidal cells are surrounded by local interneurons that can inhibit their firing pattern at various subcellular sites. Somatostatin-positive interneurons inhibit the distal dendrites in the stratum moleculare (apical tuft; orange column on the left). In contrast, parvalbumin-positive interneurons modulate pyramidal cells at more proximal dendrites and the cell body (panel A, green column on the right).

Panel B. Somatostatin-positive interneurons control information flow arriving from the entorhinal cortex. Proximal apical dendrites in CA1 receive input primarily from CA3. Thus,

parvalbumin neurons control pyramidal cell activity originating from both extrahippocampal and intrahippocampal sources.

Panel C. A loss of somatostatin neuron activity will lead to a disinhibition of the input from the entorhinal cortex.

Panel D. A loss of parvalbumin neurons will lead to asynchronous firing of pyramidal cells and increased excitatory drive from the hippocampus.