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Memoir: Pax1l

Somatostatin Interneurons
A comprehensive overview

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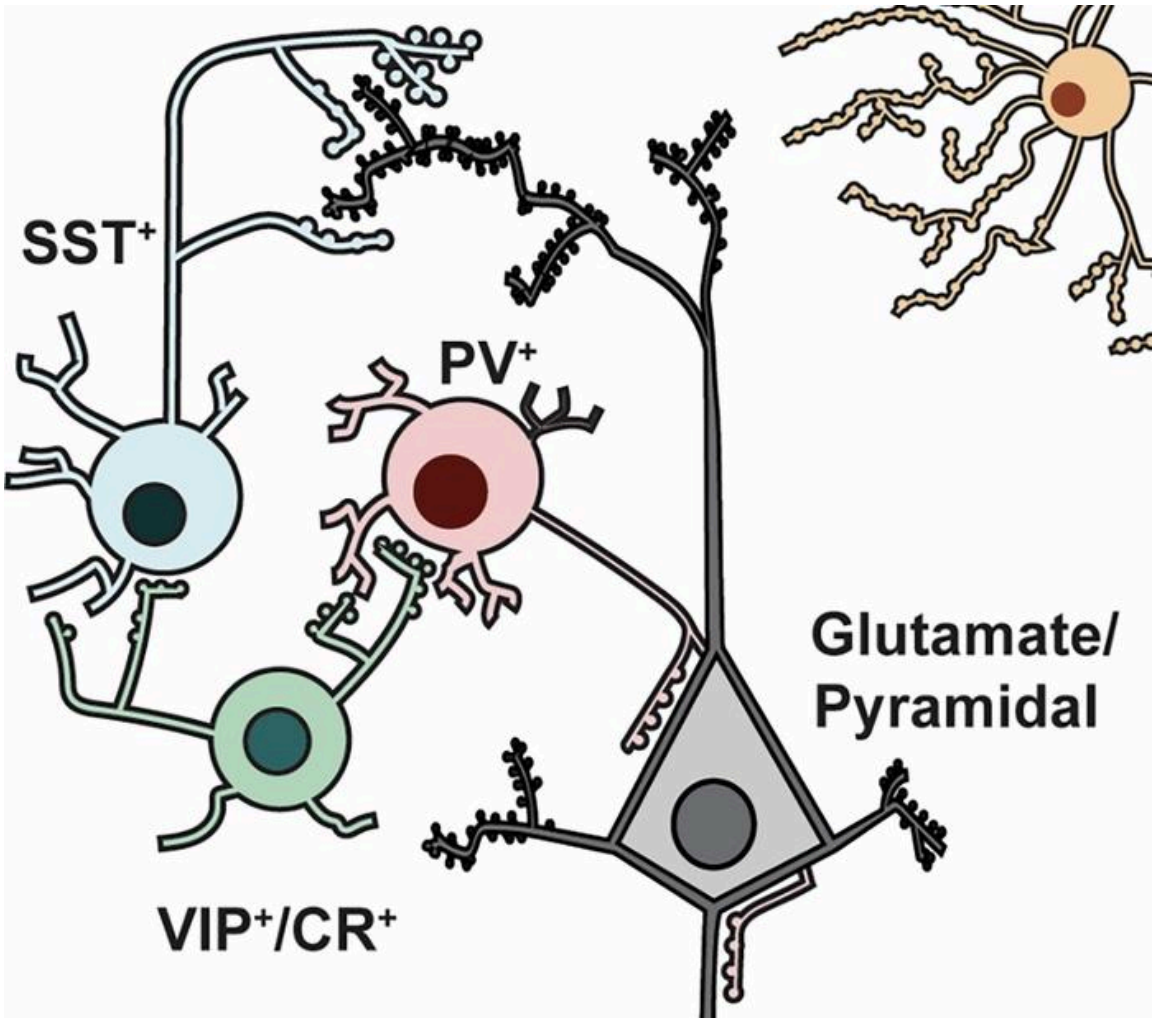
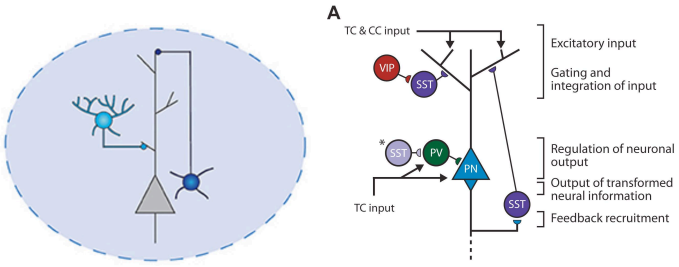


Jocapitano

INTRODUCTION

Somatostatin containing GABAergic interneurons (SST+ IN) are GABA/SST expressing inhibitory neurons that innervate Pyramidal cells (PN) across all cortical layers and Parvalbumin containing interneurons (PV+ IN) in Layer IV, thereby modulating both excitatory and inhibitory neurotransmission. While Fast Spiking PV+ IN predominantly provide inhibitory control at the soma, SST+ IN regulate neurotransmission at distal dendrites and can be exhibit diverse functional roles: direct inhibitory control at PN or disinhibition of PN via inhibition of PV+ IN in L4. They corelease Glutamate and GABA onto neurons following excitatory input at AMPA/NMDA/SST receptor sites, synchronizing spike times and fine tuning the temporal dynamics of neural activity, and they're inhibited by VIP+ IN and GABAergic input. Distinct from PV+ INs, SST+ INs can exhibit diverse morphology and electrophysiological properties (some are faster than others but preferentially they all operate during high firing rates >12hz) . This diversity allows them to modulate neuronal activity in a context dependent manner.

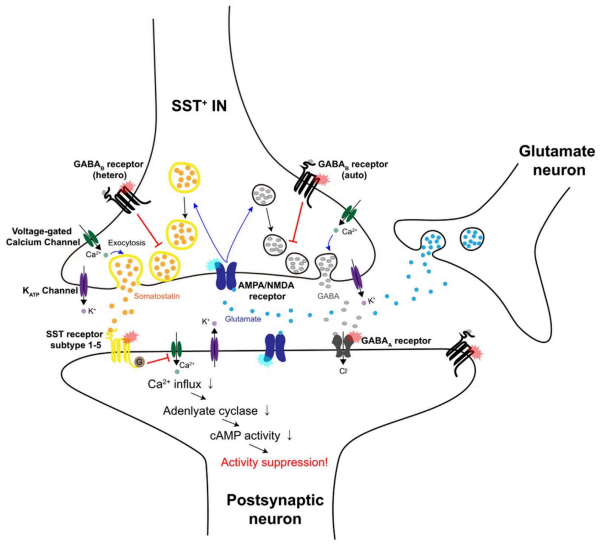
Martinotti vs Non Martinotti cells



MCs and nMCs are distinct subclasses of SST+ IN. Martinotti cells are mainly located in Layer II/III and V/VI and are characterized by long axons that target the distal apical dendrites of excitatory pyramidal neurons in Layer I, facilitating top-down inhibition and effectively modulating synaptic integration. They participate in regulating cortical rhythms (gamma and theta) and play a significant role in higher order processing.

Non Martinotti SST IN typically have axons confined to Layer IV, where they provide localized network control by inhibiting or disinhibiting pyramidal neurons and parvalbumin interneurons. Rather than long range feedback, nMCs influence short term microcircuit states by regulating firing during the initial stages of information processing.

Mechanism



SST+ IN corelease GABA and the neuropeptide Somatostatin in a calcium dependent manner. Glutamate released from excitatory synapses can evoke the release of these neurotransmitters by binding to AMPA/NMDA receptor sites on axon terminals. The GABA binds to GABAα and GABAβ receptors on the postsynaptic end, dampening neural activity. The GABAergic firing activity of SST+ IN suppresses excitatory drive to themselves via GABAβ auto/heteroreceptors. Somatostatin release requires higher intracellular calcium concentration as it's delivered in dense-core vesicles. It binds to SSTRs (mainly -2 and -3) on the postsynaptic neuron (and Astrocytes) to suppress neural activity by inhibiting calcium influx and reducing downstream cAMP. SST IN express SSTR1, providing additional modulation.

The activity of SST+ IN is nuanced: GABA and SST, although inhibitory, have different but complementary effects on synaptic activity. Phasic release of GABA is crucial for localized and precise (moment to moment, milliseconds) timing of cortical circuits, allowing synchronization of gamma and theta waves. Somatostatin provides a slower (seconds to minutes) neuromodulatory signal that extends the inhibitory effect of SST+ IN beyond the fast GABAergic IPCS to reinforce the signal, promoting LTD and long term network adaptations.

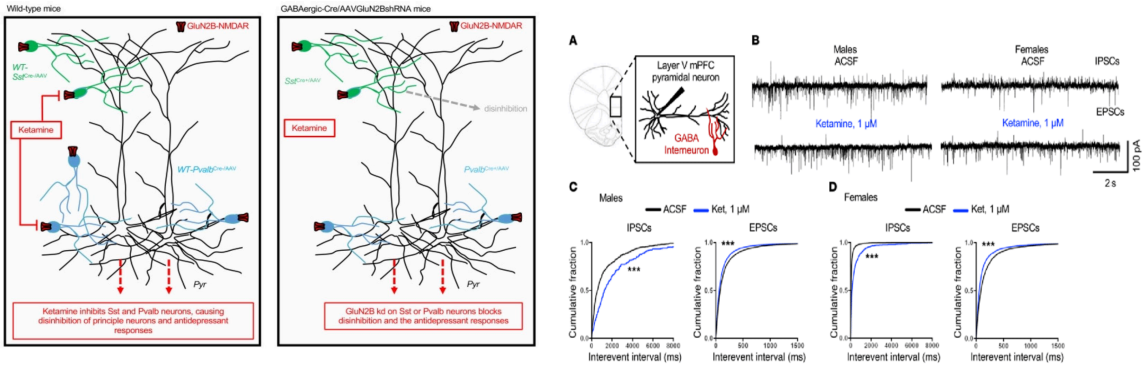
The concept of metaplasticity

Metaplasticity can be described as “the plasticity of plasticity” (in very poor terms but it delivers). It’s a process that involves homeostatic regulation of spontaneous mEPSC (independent of action potentials), which constitute the basal excitatory tone of neurons and as a consequence dynamically influence the threshold for LTP and LTD (plasticity). This principle is at the base of the antidepressant action of Ketamine: initially it reduces mEPSC but increases total EPSC. After homeostasis is reestablished, mEPCS goes back to baseline and SST might counteract these miniature spontaneous excitatory currents, ensuring the maintenance of stable basal excitation. On a higher scale , SST interneurons regulate E/I balance and adjust thresholds for future plasticity, preserving the stability of neural circuits.

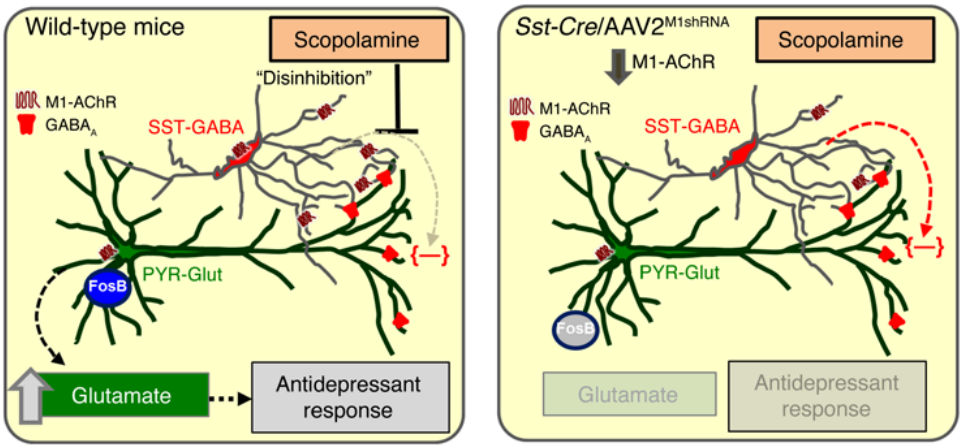
Ketamine, Scopolamine, BDNF and SOM IN

Ketamine and Scopolamine are psychoplastogens that have an important thing in common: they cause disinhibition by inhibiting of GABAergic interneurons through blockade of excitatory receptors on their surface (respectively NMDAR and M1-AChR), increasing glutamate and AMPAR mediated mTORC1-BDNF-synaptogenesis and dendritogenesis in the HPC and mPFC. It is not the only antidepressant mechanism, but it’s required and sufficient* to induce rapid, sustained effects:

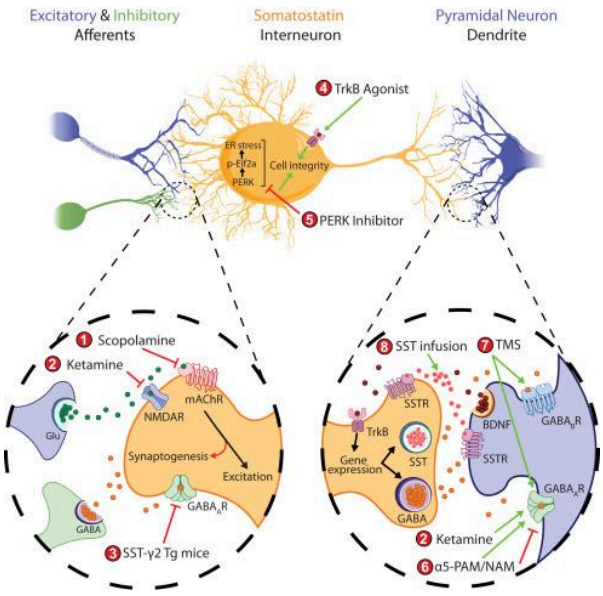
- the antidepressant actions of ketamine are blocked by NR2B NMDAR deletion in PV+ and SST+ IN but not pyramidal neurons *. Ketamine reduces IPSCs and increases whole current EPSCs



- Scopolamine works in a similar way, but through a different receptor. M1-AchR antagonism on interneurons disinhibits pyramidal neurons and induces AMPAR-mTORC1-BDNF neuroplasticity. KO of M1-AchR in GAD+ (gaba neurons) but not CamkII+ (excitatory neurons) blocked the antidepressant effect of Scopolamine *. Furthemore, M1R SST deletion also prevented stress-induced impairments in the expression of GABAergic and glutamatergic markers in the mPFC



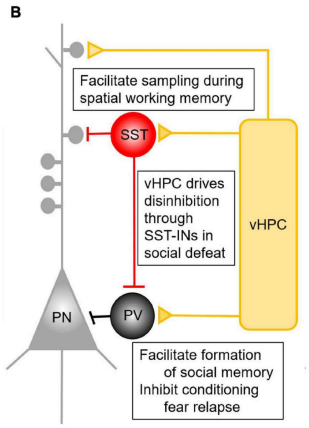
Its been hypothesized that feedback upregulation of SST+ IN is in part responsible for the sustained antidepressant effect of ketamine, and that BDNF promotes the integrity of GABAergic interneurons. From a functional standpoint, this may allow remodelling and modulation of the newly formed circuits*.



Contributions to Working Memory, functional connectivity and hippocampal memory

It appears that SST- and PV- INs participate in different phases of working memory. Unlike PV-INs, which exhibit a constant and stable increase in activity during the delay period, SST-INs exhibit more complex firing patterns: recent studies suggest that they might play a more critical role in working memory function*. They gate long range vHPC inputs to the mPFC to encode information during spatial working memory, synchronizing hippocampal-prefrontal activity. The dysfunctional GABAergic circuits in dlPFC and mPFC may underlie the working memory impairment seen in schizophrenia*. IPSCs control the fidelity of neurotransmission (signal:noise) and information processing, after all. To further support the role of interneurons in working memory, a positive correlation between GABA concentrations (thus GABAergic interneuron output) in the dlPFC and working memory capacity has been found in healthy adults*.

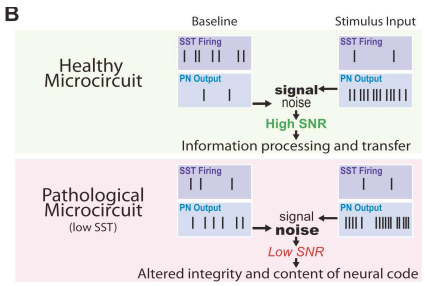
vHPC,BLA inputs to SST+ IN drive the disinhibition of mPFC by inhibiting PV+ IN, regulating social memory and behavior. But this topic is for another time...



The effects on Hippocampal LTP and memory function are much more complex, and because this writeup is a comprehensive overview on the topic, the details will be left for future writeups. The important thing to note here is that the LTP of the excitatory synapses of SST+ IN(PN—>SST), which is mGlur1 and mTOR dependent, is required for metaplasticity at CA1 hippocampal neurons and memory function*. Hippocampal rhythms (Gamma and Theta), which are well known for their importance in various memory and cortico-cortical synchronization, are mediated by somatostatin interneurons, for the most part * *.

GABAergic dysfunction in cognitive disorders

Most cognitive disorders display defects in metaplasticity and pathological GABAergic circuits. As you already know by now, SST interneurons play a critical role in regulating circuit dynamics and are implicated in various neuropsychiatric and neurodegenerative diseases (and there's so much research i don't even know how much to write, feel free to research this deeper in accordance with your interests). In depression, dysfunction of SST interneurons has been linked to impaired inhibition in cortical and hippocampal circuits and lower signal- to-noise*. In autism, the PV+/SST+ ratio is higher*. Alzheimer's disease is associated with the loss or dysfunction of SST interneurons, exacerbating the disease**. In schizophrenia, abnormalities in SST interneurons contribute to impaired cortical inhibition and disrupted dopaminergic pathways, leading to working memory and sensory processing deficits**.



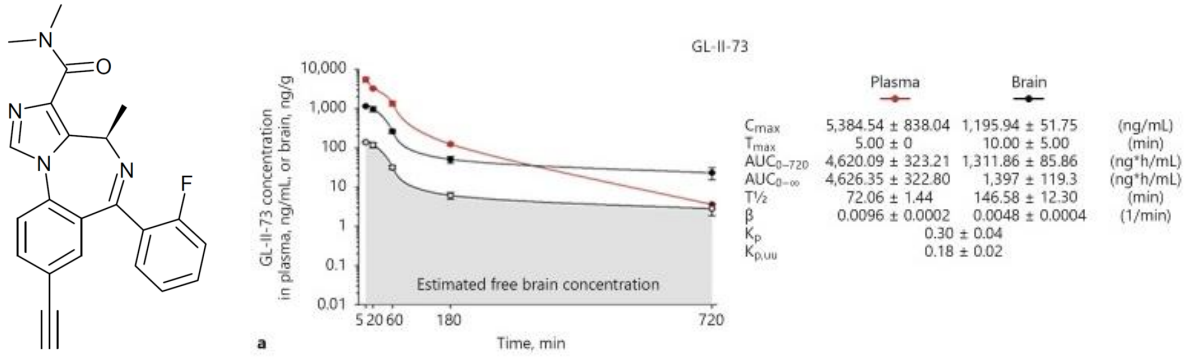
GABAα5 PAM: actionable target, promising pathway

GABAα5 subunits receive significant GABAergic input from SST+ INs, making them a viable target for disorders involving dysfunctions in inhibitory circuits and possibly cognitive enhancement, as they're arguably the most direct way to enhance the IPSCs from these interneurons. While NAMs may be useful for tasks that require disinhibition, PAMs are better for cognitive tasks where increased inhibition may increase signal to noise ratio, strengthening the salient inputs that need to be kept for high-level performances*.Therapeutically, PAMs are more promising because they address one of the primary dysfunctions (pathological GABAergic signaling such as MDD and Schizophrenia and stress/age related cognitive impairment) rather than simply disinhibiting pyramidal neurons (except in diseases characterized by excessive inhibitory tone like Down Syndrome or under conditions of neuroinflammation*). A selective GABAα5 PAM was able to reverse behavioral deficit caused by SST+ IN silencing*; the same compound ameliorated the SST+ IN impairment in a virtual model of depression* and increased spine density and apical dendritic length of L2/3 pyramidal neurons in the HPC and PFC in an age progression model though unknown mechanisms*. Disinhibition of SST+ IN results in an antidepressant and anxiolytic like brain state that's very similar to the one induced by GABAa5 PAMs*.

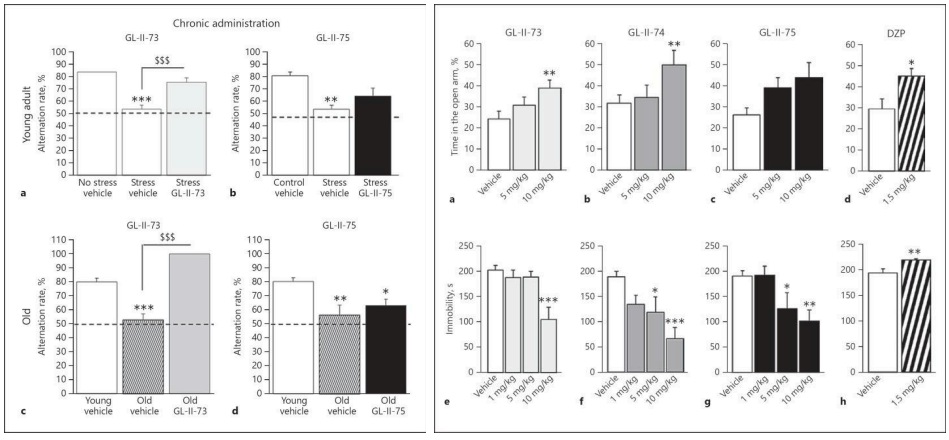
GL-II-73: an anxiolytic and antidepressant cognitive enhancer

https://pmc.ncbi.nlm.nih.gov/articles/PMC6528097/

This is the GABAα5 PAM with the most preclinical trials out of all the other benzodiazepine derivatives developed for the same purpose.



Out of the 4 ligands that were tested, despite the lower BBB penetration and relatively low half life (~2h30min), GL-II-73 showed highest selectivity for the α5 subunit and exceptionally low affinity for α1, basically eradicating the risk of motor/memory impairment. It's one of the 2 compounds that reversed working memory, stress and age related impairments in both young and old mice (the other being GL-II-75) and the only one that maintained its effects after subchronic administrations. Generally, higher potency (even at α5) result in either impairment or lack of procognitive effects due to deterioration of normal cognitive processing. Maximum anxiolytic, antidepressant and procognitive effects were observed at 10mg/kg (~50mg HED).



Alternative pathways include mglur1/5, AChRs, SSTRs, opioid system, oxytocin receptor, NMDAR modulators, neurogenics. They are not as good as GABAα5 for the following reasons: lack of data, general/indirect effects, conflicting results, unsafe.

Honorable Mention: SSTR2 & Octreotide

SSTR2 is the primary somatostatin receptor in the cortex*. As I previously mentioned, it's an inhibitory receptor that suppresses neural activity for longer periods of time than GABA by inhibiting calcium influx and reducing cAMP.

			SST receptor type				
			1	2	3	4	5
Location	Central nervous system	*cerebral cortex*					
		hippocampus					
		amygdala					
		basal ganglia					
		hypothalamus					
		olfactory bulb					
		preoptic area					
		retina					
		neuronal cilia					
	Peripheral system	*pancreas*					
		liver					
		pituitary					
		thyroid					
		lung					
		adrenal gland					
		jejunum					
		other organs	stomach, kidney	colon			heart, placenta, small intestine, skeletal muscle
Binding affinity to SST/its analogues [IC50, nM]	SST	*SST-14*	0.1-2.26	0.2-1.3	0.3-1.6	0.3-1.77	0.2-0.88
		SST-28	0.1-2.2	0.3-4.1	0.3-6.1	0.3-7.2	0.05-0.4
	CST	*Cortistatin-14*	2.1	0.5	3.8	18.2	0.9
		Cortistatin-17	0.25-7.0	0.6-0.9	0.4-0.6	0.5-0.6	0.3-0.4
	SST analogues	*Octreotide*	280-1140	0.38-0.56	7.1-34	>1000	6.3-7
		Pasireotide	9.3	1	1.5	>100	0.16
		Lanreotide	180-2330	0.54-0.75	14-107	230-2100	5.2-17
		Vapreotide	>1000	0.2-5.4	31	45	0.7
		Somatoprim	>1000	3	>100	7	6
Neurological disorder		*Alzheimer's disease (AD)*	-	↓	↑	↓↓	↓↓
		Parkinson's disease (PD)	↓ (but, not specifically identified)				
		Hungtinton's disease (HD)	↓	↑ (compensatory for NMDA ↑)	N.D.	N.D.	↓
		Major mood disorder (MDD)	N.D.	↓*; anxiety, depression	↓*; depression	N.D.	N.D.
		Schizophrenia (SCZ)	N.D.	↓	N.D.	N.D.	N.D.

As you can see from the image above, SSTR2 is implicated in a lot of cognitive and neurodegenerative diseases. This is in line with the reduction of the neuropeptide itself (SST) seen in most of these conditions (in AD, patients lose up to 70% of their SST INs).

Octreotide is a Somatostatin (SST14) analog with good affinity for SSTR2. In human Alzheimer's disease patients and even older healthy subjects, it enhanced memory (alone or in conjunction with insulin)*.

Want to hear something mind blowing? Octreotide analogs are able to increase striatal dopamine levels by up to 28 fold (18x for SSTR2 selective ligands) and produce anxiolysis almost comparable to Diazepam, through glutamatergic mechanisms (likely an interplay of inhibition of PV+ INs and PNs and disinhibition of PNs), while suppressing apoptosis and oxidative stress**.

Somatostatin is also increased during neuronal development to support axon outgrowth by increasing MAP2 (microtubule associated protein)**.

Unfortunately, activation of SSTRs produces an undesirable shift in the way hippocampal memories are processed, leading to impairment in some areas of cognition*.

Appendix

GABA: major inhibitory neurotransmitter

Glutamate: major excitatory neurotransmitter

PN-Pyramidal Neuron: excitatory neuron that extends across all layers of the cortex. Can be excited or inhibited

(GABAergic) interneuron: inhibits Pyramidal Neurons or other interneurons. They can express various neuropeptides (such as PV parvalbumin, SST somatostatin, VIP vasointestinal peptide)

EPSC: excitatory post synaptic current mEPSC: miniatureEPSC

IPSC: inhibitory post synaptic current

mPFC: medial prefrontal cortex

dlPFC: dorsolateral prefrontal cortex

HPC: hippocampus

LTP: long term potentiation

LTD: long term depression

mTOR: regulates cell proliferation, autophagy, apoptosis, synaptic plasticity (BDNF)

NMDAR, AMPAR: Glutamate receptors

M1 AChR: muscarinic acetylcholine receptor

cAMP: intracellular messenger

Concluding remarks

This original writeup provides a general overview on a topic that everyone should be familiar with before going deeper into the rabbit hole, and a product synthesis recommendation at the end; while the first part may seem pedantic, it's necessary to understand the complex dynamics of inhibitory circuits in the brain . There’s certainly a lot more to it, but this should be enough to guide yourself through papers and get a basic understanding on how inhibitory circuits in the brain work and how they affect cognitive processes. I honestly wish i had something like this when starting out, it would have saved me a lot of time and confusion.