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Opinion

Parvalbumin interneuron cell-to-network plasticity: mechanisms and therapeutic avenues

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Alzheimer's disease (AD) and schizophrenia (SCZ) represent two major neuropathological conditions with a high disease burden. Despite their distinct etiologies, patients suffering from AD or SCZ share a common burden of disrupted memory functions unattended by current therapies. Recent preclinical analyses highlight cell-type-specific contributions of parvalbumin interneurons (PVIs), particularly the plasticity of their cellular excitability, towards intact neuronal network function (cell-to-network plasticity) and memory performance. Here we argue that deficits of PVI cell-to-network plasticity may underlie memory deficits in AD and SCZ, and we explore two therapeutic avenues: the targeting of PVI-specific neuromodulation, including by neuropeptides, and the recruitment of network synchrony in the gamma frequency range (40 Hz) by external stimulation. We finally propose that these approaches be merged under consideration of recent insights into human brain physiology.

Highlights

Rescuing memory deficits remains a major challenge in treating Alzheimer's disease (AD) and schizophrenia (SCZ).

Parvalbumin interneurons (PVIs) mediate network activities relevant to memory functions. Current research suggests that the ability of PVIs to functionally adapt upon increased network activity underlies the generation of memories. The cell-type-specific interaction of neuronal plasticity on the cellular and network level (PVI cell-to-network plasticity) is a promising target in addressing memory deficits.

Two clinically accessible strategies targeting PVI plasticity have emerged for the treatment of memory deficits in AD and SCZ: PVI-specific neuromodulation and high-frequency stimulation in the gamma frequency range (40 Hz).

Research into clinically assessing PVI cell-to-network plasticity in humans will be essential to transfer current findings into clinical practice.

Memory deficits in AD and SCZ, and therapeutic avenues targeting PVI cell-to-network plasticity

AD and SCZ are distinct neuropsychiatric diseases in terms of their etiology, underlying pathology, and disease-specific symptoms. However, they share a common, clinically unaddressed burden of impaired memory processes, which are accompanied by clinically observable disruptions of neuronal oscillations in the gamma frequency range (30–80 Hz) or **gamma oscillations** (see Glossary). The high prevalence and disease burden of AD and SCZ drive efforts to identify effective and scalable therapeutic concepts [1,2]. However, current therapeutic strategies fail to reinstate memory deficits in either disease. This has motivated the pursuit of novel avenues considering recent advances in understanding the physiology of memory processes and how they are affected in states of disease.

In this opinion we reiterate the need to address the memory gap left in AD and SCZ treatments, and highlight evidence implicating a particular class of inhibitory interneuron expressing parvalbumin – **parvalbumin interneurons (PVIs) –** as a promising target. We argue that PVIs support memory functions by increasing their cellular excitability (**PVI plasticity**), which during memory consolidation translates to the network level as an increased spectral amplitude ('power') of gamma oscillations [3] (PVI **cell-to-network plasticity**). We review findings implicating functional deficiencies of PVI cell-to-network plasticity in memory deficits and identify two preclinically successful strategies for rescuing these in AD and SCZ: the cell-type specific **neuromodulation** of PVIs and the induction of neuronal oscillations. Molecular targets of PVI neuromodulation, including **metabotropic glutamate receptor 5 (mGluR5)** and **neuropeptides**, are subsequently explored as pharmacologically accessible targets of PVI plasticity alongside

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recently developed **gamma frequency stimulation** paradigms imposing neuronal oscillations. Finally, we propose that merging approaches targeting PVI neuromodulation and gamma frequency stimulation may ease the reinstatement of memory functions in AD and SCZ, and argue that future therapeutic strategies will profit from intensified analyses of human brain cellular and network physiology.

The memory gap in AD and SCZ, and PVI impairment as a common untreated mechanism

Cognitive disabilities represent a severe burden for patients suffering from neuropsychiatric diseases. Beyond their direct effects on patient health and independence, limitations of cognitive abilities further expose patients and their dependents to socioeconomic risk and additional mental health problems. However, available therapeutic options rarely reinstate cognitive abilities. Memory processes – including the storage and retrieval of information – remain mostly untreated in patients suffering from diseases as diverse as AD and SCZ.

AD, the most common form of dementia, is marked by progressive memory loss upon accumulation of amyloid-β (Aβ) and ensuing neurodegeneration. While recent Aβ-targeting antibodies show promise in slowing disease progression, they fail to restore deficits in memory functions [4], a fate shared by earlier, neurotransmitter-targeting approaches such as the N-methyl-D-aspartate receptor (NMDAR) antagonist memantine and the cholinesterase inhibitor rivastigmine. SCZ, on the other hand, presents with a mix of psychotic, anhedonic, and cognitive symptoms, the latter including both episodic and working memory deficits. Whereas neurodegeneration can occur in SCZ patients, traditional disease models implicate disruptions of global neurotransmitter systems – including glutamate, γ-aminobutyric acid (GABA), and dopamine – as causal in symptom onset [5]. More recent theories elaborate on this, pointing toward genetic, immunological, and oxidative stressors pre-dating changes to neurotransmission [6–8]. Despite this heterogeneous pool of possible causes, current treatments center on pharmacologically antagonizing broadly expressed **G-protein-coupled receptors (GPCRs)**, for example, dopaminergic, Gi-coupled D2 receptors. However, these primarily target psychotic symptoms, with limited efficacy towards anhedonic and cognitive symptoms [9].

Successful memory processes require the concerted activities of networks of neurons resulting in the induction of neuronal plasticity (Box 1). To this end, associative cortical areas, particularly the hippocampus and prefrontal cortex (PFC), have emerged as central, interdependent hubs of memory processing [10,11]. In the cases of AD and SCZ, it is therefore plausible that distinct causes such as neurodegeneration and disrupted neurotransmission mechanistically converge on impairing the coordination of network activities in these regions. In line with this, disruptions of gamma oscillation power have emerged as a common, clinically accessible biomarker in the hippocampus and/or PFC of AD and SCZ [12,13]. On the cellular level, this is mirrored by pathological changes in PVI function, restricting the amount of GABAergic inhibition provided to the network and thereby prohibiting synchronization at gamma frequencies [14,15]. Therefore, impaired cognitive functions in AD and SCZ may be due to a lack of effective inhibitory control provided by PVIs, which physiologically is maintained through neuronal plasticity. Recent proposals argue that either supporting the regeneration of neuronal populations [16] or pharmacologically modulating GABAergic transmission [17] may suffice to reinstate cognitive functions. In the following section, we add to this by focusing on the physiological mechanisms supporting memory processes in health, which engage plasticity in PVIs and enhance neuronal oscillations by means of cell-to-network plasticity.

Glossary

Biased mGluR5 PAMs: pharmacological agents specifically enhancing the Gq-protein-dependent response of mGluR5 activation.
Cell-to-network plasticity: translation of plasticity obtained by a molecularly distinct cell type to specific neuronal network activity states.
Contextual fear conditioning (CFC): associative memory task in which the subject experiences pain in a specific, recognizable environment. Upon successful conditioning and re-exposure to the same environment, subjects display fear-associated behavior (e.g., freezing in mice).
5 x Familial Alzheimer's disease (5XFAD) model: a genetic mouse model of AD carrying five common mutations linked to AD and resulting in an aggressive AD phenotype apparent within 2–6 months of age.
G-protein-coupled receptors (GPCRs): transmembrane proteins widely expressed in the central nervous system and a primary site of action for neuromodulation. Upon ligand binding, an intracellular metabotropic cascade is kickstarted. Depending on the involved G-protein subtype, this raises intracellular calcium and protein kinase C activity (Gq-protein) or respectively increases (Gs-protein) or decreases (Gi-protein) cAMP levels.
Gamma entrainment using unspecific sensory stimuli (GENUS): application of sensory stimuli (e.g., light flicker or sound) at 40 Hz evokes a stereotypical network oscillation in the corresponding sensory cortex of test subjects, which further entrains downstream associative cortices.
Gamma frequency stimulation: a collective term summarizing a variety of methods evoking neuronal synchrony at frequencies in the gamma rhythm (most commonly 40 Hz). These include repetitive transcranial magnetic stimulation (rTMS), transcranial electrical stimulation (tES), and gamma entrainment using unspecific sensory stimuli (GENUS).
Gamma oscillations: extracellularly recorded, rhythmic fluctuations of the voltage field potential with peak frequencies ranging from 30 Hz to 120 Hz, which accompany cognitive functions across the cerebral cortex.
Human amyloid precursor protein (hAPP) model: a genetic mouse model of AD carrying two common mutations

Box 1. Gamma oscillations, ensembles, and engrams underlying memory functions

Neuronal oscillations arise from the synchronized activities of local neuron populations and are detected as periodic fluctuations in extracellular recordings, for example, electroencephalograms (EEGs) or magnetoencephalograms (MEGs). These are strong predictors of cortical state, amongst which gamma oscillations (30–120 Hz) are especially associated with higher cognitive functions, including the encoding and retrieval of memory processes. Single neurons phase-lock their firing rates to preferred gamma periods and create ensembles of coactive neurons, giving rise to the assumption that, by parsing the activities of individual cells and binding them on millisecond time scales, gamma oscillations create periods of increased information transfer [116]. Mechanistic analyses of gamma oscillations reveal that they emerge from reciprocal synaptic interactions between glutamatergic, excitatory pyramidal neurons and GABAergic, inhibitory interneurons, particularly fast-spiking PVIs [117]. More recent analyses therefore argue that gamma oscillations represent a network correlate of cellular activity rather than a fixed network state imposed on the cellular population [118]. Regardless, anomalies of gamma oscillation magnitude ('power') are consistently reported in neuropsychiatric diseases, rendering them a widely accepted biomarker for cognitive function.

To store information generated by ensembles, an enduring, physical representation of their coactivation must be formed, which enables them to adequately reinstate said information. This physical representation, the neuronal engram, is argued to underlie lasting memory processes [119]. Neurons recruited during learning (i.e., the acquisition of information) undergo transcriptomic changes that render them more excitable and strengthen the synaptic connections between them [120]. Recall of this information is disturbed when engram neurons are inhibited and, conversely, their artificial activation retrieves the memory on demand [119]. Importantly, in any given neuronal population, the strength of engrams, and therefore memory performance, is equally determined by the suppression of nonparticipating cells by synaptic, GABAergic inhibition [121]. Understanding the creation, maintenance, and overwriting of engrams represents a core discipline of current neuroscientific research, promising a neuronal basis for understanding memory deficits in states of disease.

To date, lacking experimental tools to track engram neurons during extracellular oscillations, evidence linking the emergence of engrams to prior gamma oscillations remains indirect. However, both gamma oscillations and engram formation are mechanistically related by their reliance on PVI-mediated inhibition [45,117]. The finding that gamma oscillations induce long-lasting synaptic plasticity in selected, participating neurons [51] further suggests that memory engrams may at least in part originate from their prior activation during states of gamma activity (Figure I).

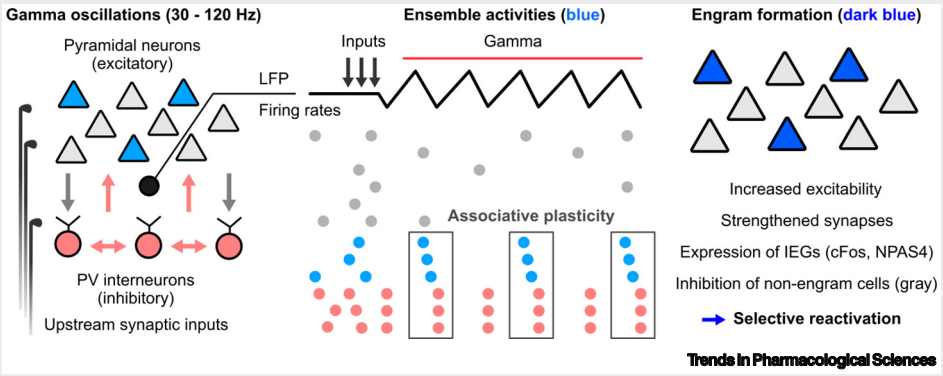

Figure I. Gamma oscillations, neuronal ensembles, and engrams. Left: schematic illustrating the generation of gamma oscillations. Upon activation from external inputs (dark synapses), groups of interconnected, excitatory pyramidal neurons and inhibitory parvalbumin (PV) interneurons coactivate. The cumulative extracellular currents are recorded with a local field potential electrode (LFP, black). Center: overlay of field gamma oscillations and concomitant neuronal firing rates. During gamma activity, a subset of ensemble pyramidal neurons (blue) preferably coactivate during the descending (i.e., depolarizing) oscillatory phase and drive a burst of PV interneuron firing, facilitating associative plasticity between the participating cells. Right: plasticity in the participating cells drives anatomical changes in the ensemble population (listed), including enhanced cellular excitability and the expression of immediate early genes (IEGs). The engram formed thereby is subsequently more likely to be reactivated upon adequate stimulation.

Cell-to-network plasticity of parvalbumin interneurons underlying memory processes

PVIs are highly interconnected with the surrounding neuronal microcircuit, integrating converging glutamatergic inputs and providing widespread, divergent inhibition [18]. Once activated, this architecture supports network phenomena underlying the formation of memories on two time

of hAPP. During postnatal development, these animals increasingly express the pathological Aβ40 and Aβ42 strains across the entire brain and begin to exhibit AD-defining symptoms after 6–12 months.

Intrinsic excitability: measure for the responsiveness of a neuron to generate action potentials at given input currents; it is determined mainly by biophysical membrane properties, including membrane capacitance, transmembrane resistance, and the expression of voltage-gated sodium and potassium channels, the latter including Kv1.1.

LgDel+/–: designation for a genetic mouse mutant mimicking the 22q11 microdeletion 'DiGeorge' syndrome observed in humans. In humans, 22q11 microdeletion confers a high genetic risk for neuropsychiatric diseases, including SCZ (roughly 30%) and autism spectrum disorder (roughly 25%). Mice heterozygous for the LgDel mutation display core anatomical and behavioral features of SCZ and are routinely used as model system to elucidate mechanisms underlying disease pathology and putative treatments.

Long-term potentiation (LTP): increase in synaptic transmission variably due to changes in neurotransmitter release probability, the number of synaptic release sites, or the expression of neurotransmitter receptors. Upon adequate stimulation, increases are observed within minutes and can last for days. LTP induction is variably gated by neuromodulation.

Metabotropic glutamate receptor 5 (mGluR5): a Gq-coupled GPCR abundantly expressed across the central nervous system. Upon binding of extracellular glutamate, a neuromodulatory cascade is evoked, increasing intracellular calcium and phosphorylation levels and depolarizing excitable cells.

Neuromodulation: various forms of neuronal signaling (e.g., dopamine, serotonin, neuropeptides) which act by tuning the responsiveness of target neurons towards synaptic transmission (i.e., by gating LTP).

Neuropeptides: a heterogeneous class of signaling molecules spanning up to 100 amino acids and often co-released from 'dense core vesicles' upon presynaptic activation at higher frequencies. Preferably released by GABAergic interneurons, neuropeptides (e.g., oxytocin, Nrg1, NPTX2, Scg2) act

scales: the ad hoc generation of network gamma oscillations, and the shaping of lasting neuronal engrams (Box 1). This capability depends on the level of cellular excitability PVIs express, which is subjected to activity-dependent changes (PVI plasticity) (Figure 1A) [19]. PVI plasticity, as described in the following subsections, is gated by neuromodulation and effectively guides the capability of PVIs to form memory-supporting network phenomena (cell-to-network plasticity). Scrutinizing the mechanisms of this interaction will reveal PVI-specific targets for the treatment of memory dysfunctions in later sections.

Three layers of PVI plasticity

Within minutes upon activation at high frequencies (30–100 Hz), PVIs adapt their synaptic input/output properties by a process of **long-term potentiation (LTP)** of their glutamatergic inputs and

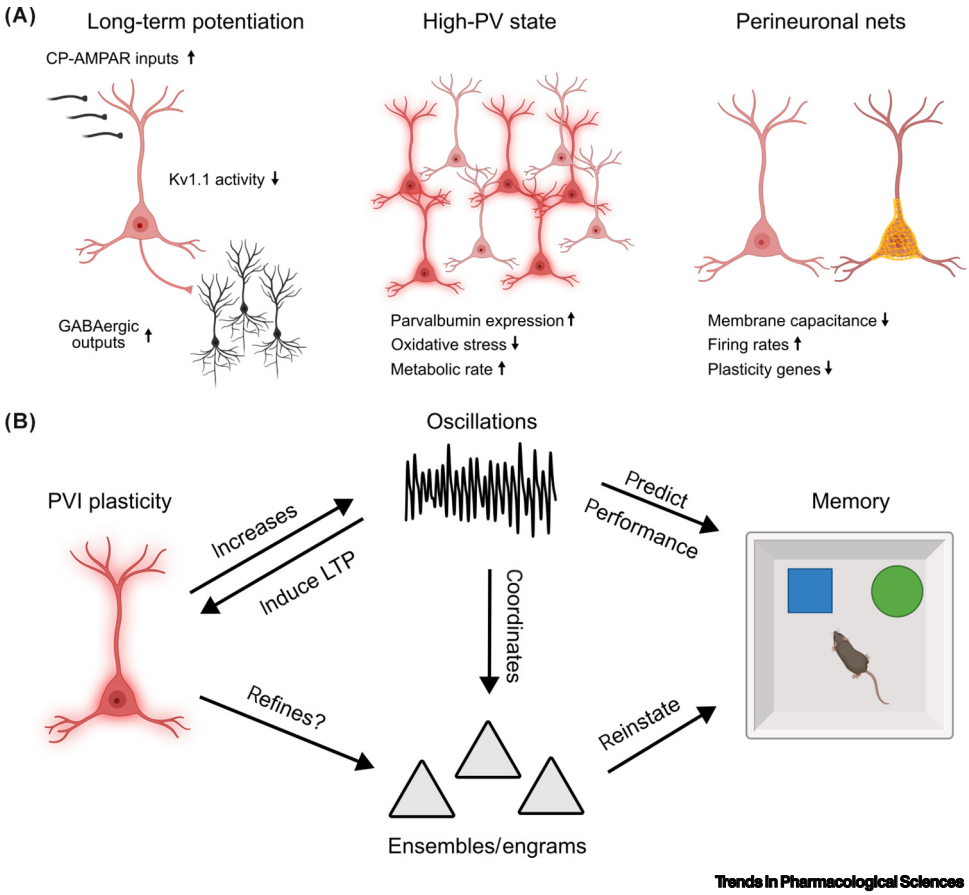

Figure 1. Cell-to-network plasticity of parvalbumin interneurons underlying memory formation. (A) Parvalbumin interneurons (PVIs) express plasticity on three scales. Left: long-term potentiation (LTP) of PVI synaptic properties. LTP increases the efficacy of glutamatergic inputs expressing calcium-permeable AMPA receptors (CP-AMPARs, black synapses), reduces Kv1.1 activity, and increases transmission at the GABAergic output synapse (red synapse) onto local pyramidal cell populations. Center: during memory consolidation, a large subset of PVIs undergo increased expression of parvalbumin (highlighted cells), reducing oxidative stress and increasing their metabolic rate. Right: perineuronal net (PNN) (yellow net) generation around a subset of PVIs alters membrane properties, increases their firing rates, and restricts the expression of plasticity-associated genes. (B) Cell-to-network transfer of PVI plasticity to memory processes. PVI plasticity emerges from a reciprocal relationship with neuronal network oscillations, with oscillations inducing PVI-LTP and oscillations subsequently increased. Improved inhibition provided by PVIs refines the selection of ensemble neurons, the activities of which are coordinated by local oscillation dynamics. The amplitude of oscillations predicts the success of subsequent recall, depicted here in a novel object recognition task, which requires the formation of persistent neuronal engrams. Images created with BioRender.

as specialized neuromodulators via GPCRs or tyrosine kinases.

Parvalbumin interneurons (PVIs): the most abundant subclass of GABAergic interneurons in the central nervous system characterized by high action potential frequencies (also 'fast spiking interneurons') and the expression of the calcium-binding antioxidant parvalbumin.

Perineuronal nets (PNNs): extracellular matrix components generated by and encapsulating PVIs. PNN expression accompanies the closing of critical periods in cortical maturation, maximizes the excitability of PVIs, and reduces oxidative stress.

PV state: a measure of the ratio of PVIs expressing low, intermediate, or high levels of parvalbumin protein at a given time point. It co-varies with recent experience and learning and is inclined towards low PV states in animal models of neuropsychiatric disease.

PVI plasticity: cellular processes which enhance or decrease the excitability of PVIs in the short to long term. It includes changes in ion channel expression, transcriptional changes, and anatomical adaptations, the latter including the generation of synapses and the expression of PNNs.

Repetitive transcranial magnetic stimulation (rTMS): a noninvasive brain stimulation method using magnetic coils to rhythmically induce electrical currents in adjacent cortical regions.

Transcranial electric stimulation (tES): a noninvasive brain stimulation method applying currents (tACS, alternating current; tDCS, direct current) through electrodes attached to the scalp.

long-term plasticity of their **intrinsic excitability** [19,20]. PVI-LTP requires activation of calcium-permeable AMPA receptors (CP-AMPARs), Gq-coupled group I mGluRs, protein kinase C, and the mainly PVI-specific γ-subvariant of calcium/calmodulin-dependent protein kinase II (γ-CaMKII) [21–24]. Increased CP-AMPAR conductance and reduced activity of the voltage-gated potassium channel Kv1.1 [25] subsequently render PVIs more excitable, elevating their firing rates and increasing GABA release onto postsynaptic targets. PVI output synapses, too, undergo LTP via different agents, including neuropeptides derived from secretogranin 2 (Scg2) [26,27].

The increased firing rates and neurotransmitter turnover following PVI-LTP necessitate a corresponding shift in metabolic rate. This is mirrored in the expression levels of the calcium-binding antioxidant protein parvalbumin itself [28]. Parvalbumin expression intermittently increases amongst PVIs (high-**PV state**) in the hours following **contextual fear conditioning (CFC)** and returns to baseline values upon successful memory consolidation (intermediate-PV state) [29]. This learning-related molecular plasticity lasts for up to 12 h and requires dopaminergic, Gs-coupled D1 receptors (D1Rs) and protein kinase A [30].

In a final, long-lasting measure, PVIs regulate their excitability by generating **perineuronal nets (PNNs)** of extracellular matrix, reducing membrane capacitance and increasing input resistance [31]. PNN expression covaries with the state of PVI firing rates [32,33], is negatively regulated by the group I mGluR mGluR5 [34] and absent from spine-carrying dendritic segments in adult PVIs, speculated to harbor preferred sites of plasticity [35]. This indicates a bimodal, restrictive effect toward subsequent PVI plasticity and is highlighted by the negative correlation between PNN expression and plasticity-associated genes [36]. PNNs render PVIs less vulnerable to oxidative stress [37] and are vital to the long-term storage of memories [38,39].

The maturation of PNNs marks the end of functionally 'critical periods', limiting subsequent cortical adaption processes to changes in sensory landscapes [40]. The acquisition of PVI excitability may therefore saturate the amount of information a cortical network can process. To retain a capacity for new memories or overwrite existing ones, countermeasures exist reducing PVI excitability: long-term depression reduces CP-AMPAR conductance [19,41], environmental enrichment resets a low-PV state [28], and PNNs are degraded upon long-lasting inactive periods [32]. Associative cortical areas required for higher-order memory tasks (e.g., the PFC and hippocampus) express lower parvalbumin/PNN co-localization rates (50%) than their primary sensory counterparts (70%) [36]. Ongoing memory functions may therefore require a steady state of on-demand PVI plasticity entailing downstream effects on neuronal network activity.

Consequences of PVI plasticity on the network level

Genetically ablating the molecular anchors of PVI plasticity (CP-AMPARs, mGluR5, Scg2, PNNs) variably disrupts neuronal network activity and/or memory performance [27,42–44]. Recent investigations scrutinizing CFC acquisition (immediately following conditioning), consolidation (<24 h post-conditioning) and recall (>24 h post-conditioning) shed further light on the physiological contributions of PVIs towards memory formation. Notably, for successful recall, hippocampal PVIs must have sufficiently expressed parvalbumin and PNNs prior to conditioning [45] and must activate in both the hippocampus and PFC during memory acquisition and consolidation [30,46]. Following acquisition, the consolidation phase is accompanied by both a high-PV state [30] and increased amplitudes of sleep-associated oscillations, including theta (3–7 Hz) and gamma (30–120 Hz) frequencies [24,47] as well as increased hippocampal–PFC oscillatory coupling [46]. Depriving animals of either D1R signaling or sleep during this process prevents subsequent recall, which is (respectively) reinstated by rescuing cAMP activity in PVIs [30] or inducing oscillations by optogenetic PVI recruitment [48] in the hippocampus. Memories generated

under these conditions last in mice for several weeks [46], demonstrating an enduring functional impact of PVI plasticity once consolidation has taken place.

How do PVI plasticity and neuronal oscillations interact to generate long-lasting memories? A possible explanation lies at the PVI input synapse. Following CFC, γ-CamKII-dependent phosphorylation of the AMPAR subunit GluR1 is upregulated in hippocampal PVIs, indicating recent PVI-LTP and putatively facilitating PVI recruitment, sleep-associated theta and gamma oscillations and finally memory recall [24]. Mechanistically, augmented oscillations stabilize the coactivation of ensemble neurons [47] underlying the formation of sparse neuronal engrams, therefore completing memory formation (Box 1). Intriguingly, the effective GABAergic control PVIs exert over engram sparsity diminishes upon recall, instead being maintained by non-fast-spiking, cholecystokinin-expressing interneurons [49,50] and coinciding with the return of an intermediate-PV state. In line with this, interventions preventing PVI activation fail to prevent memory recall once the vulnerable period of consolidation has passed [46]. A specific allocation of PVI plasticity towards memory generation, rather than upkeep, may serve to conserve a plastic capacity for the encoding of future memories.

This indicates a bidirectional, dual requirement of PVI-specific neuromodulation (mGluR5 and D1Rs) and enhanced neuronal oscillations in memory formation, as formalized by two *ex vivo* findings from our group: (i) induction of neuronal gamma oscillations is sufficient to induce mGluR5-dependent LTP onto pyramidal neurons and PVIs [51], and (ii) increased gamma power upon reactivation is subsequently mediated by PVI-specific Gq- and Gs-activation [3]. In concert with the *in vivo* findings summarized earlier, this completes a mechanistic profile of PVI cell-to-network plasticity underlying the acquisition and consolidation of memories in mature cortical networks (Figure 1B). In the following section we will explore how deficiencies in this profile are apparent in AD and SCZ and can be specifically targeted in preclinical disease models to reinstate memory performance.

PVI cell-to-network plasticity underlying memory deficits in AD and SCZ

Postmortem tissue from patients suffering from either AD or SCZ consistently displays reductions in PVI cell count and the expression of parvalbumin and/or PNNs [14,15]. Whereas the latter points to a lack of ongoing PVI plasticity, postmortem samples permit neither functional cellular analyses nor conclusions about the etiology of disease. Corresponding animal models of AD and SCZ routinely express deficient PVI excitability, parvalbumin, and/or PNN expression. This translates to synaptic dysbalances between excitation and inhibition underlying network oscillations, which finally predicts and accompanies later memory deficits [14,15] (Figure 2A). Conversely, experimental approaches reinstating memory performance in these models preferably target the two axes of PVI cell-to-network plasticity: neuromodulation and the induction of network oscillations. This is highlighted in two comprehensive studies in respective animal models of AD and SCZ: in the **human amyloid precursor protein (hAPP) model** of AD, downregulation of the voltage-gated sodium channel Nav1.1 leads to decreased PVI intrinsic excitability, aberrant hippocampal gamma oscillations, and severe deficits in memory formation [52]. Overexpressing Nav1.1 selectively in PVIs by either genetic modification or targeted PVI transplantation in the early postnatal period reduces deficits of cellular, network and long-term memory functions spanning days [52,53]. In the **LgDel+/–** model of SCZ, disproportionate D2R activity causes reduced PVI firing rates and an inert low-PV state in adulthood, which are mirrored by progressively reduced gamma oscillation magnitude and working memory performance. Selectively blocking hippocampal or PFC D2Rs in adolescence prevents subsequent PVI plasticity deficits and network symptoms weeks later in adulthood [54]. The apparent specificity of PVI recruitment for successful treatment is further supported by experiments activating genetically designed receptors exclusively in PVIs (Figure 2B).

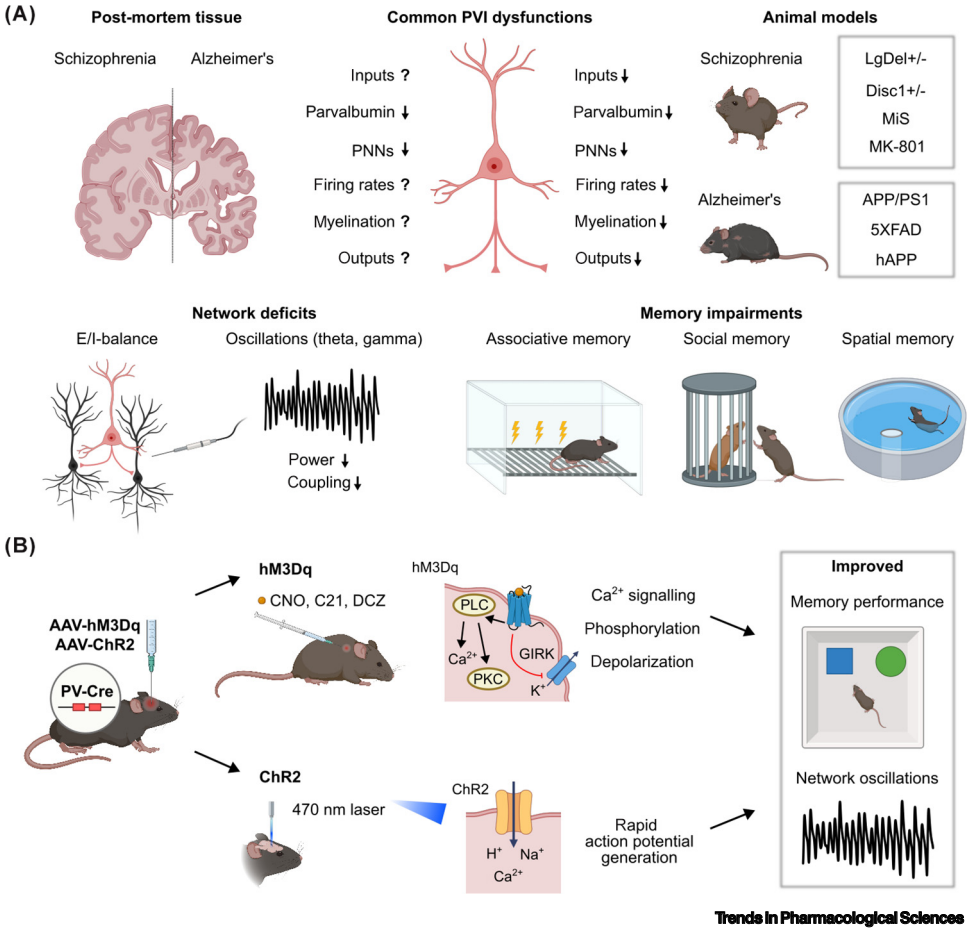

Figure 2. Parvalbumin interneuron (PVI) cell-to-network plasticity is disturbed in animal models of schizophrenia (SCZ) and Alzheimer's disease (AD) and can be reinstated by selective chemo- or optogenetic PVI recruitment. (A) Top: postmortem tissue samples of SCZ and AD are morphologically distinct (left) yet share a common cellular pathology in PVI dysfunctions (center), which are reproduced in respective animal models of SCZ and AD (right). Bottom: PVI dysfunctions at differing cellular structures (listed earlier) translate to a dysbalance between network excitation and inhibition (E/I balance) and are marked by deficient network oscillations, especially in the theta and gamma band. This is accompanied by associative, social, and spatial memory impairments. (B) Cell-type-specific treatments targeting PVIs. Left: in diseased animals, viral expression (adeno-associated virus, AAV) of either the Gq-designer receptors exclusively activated by designer drugs (DREADDs) hM3Dq or the light-activated cation channel channelrhodopsin 2 (ChR2) permits the specific activation of PVIs. Top: PV-hM3Dq activation with the selective compounds clozapine-N-oxide (CNO), Compound 21 (C21), or deschloroclozapine (DCZ) recruits a Gq-cascade in PVIs, depolarizing them by blockade of G-protein-coupled inwardly rectifying potassium channels (GIRK) and increasing intracellular calcium and phosphorylation levels via phospholipase C (PLC) and protein kinase C (PKC). Bottom: PV-ChR2 activation by blue light (470 nm) opens the channel pore, permitting the entry of sodium (Na^+), calcium (Ca^{2+}), and protons (H^+). Both PV-hM3Dq and -ChR2 activation restore memory performance and oscillations in diseased animal models. Abbreviations: 5XFAD, 5 x Familial Alzheimer's disease; APP/PS1, human amyloid precursor protein/presenilin 1 mutant; MiS, maternal infection syndrome; PNNs, perineuronal nets. Images created with BioRender.

Exogenous GPCRs (designer receptors exclusively activated by designer drugs, DREADDs) have emerged as powerful, specific tools to study neuropsychiatric symptoms. Activation of Gi-DREADDs in PVIs reduces intracellular cAMP levels, prevents CFC-induced plasticity of neural oscillations and memory formation [46,47], and – applied chronically to the PFC – induces SCZ-typical neuroanatomical and behavioral symptoms [55]. Conversely, activation of Gq-DREADDs raises intracellular calcium and phosphorylation levels in PVIs and supports activity-dependent

plasticity of gamma oscillations [3]. This is sufficient to rescue memory deficits, ensemble dynamics and network oscillations in LgDel+/– animals [56], with similar results in animals undergoing pharmacologically induced psychosis [55]. In mice chronically treated with phenylcyclohexyl piperidine (PCP), Gq-DREADD activation even displays an added beneficial effect on working memory deficits towards sole administration of the D2R-antagonist olanzapine [57].

Alternatively, recruitment of PVI firing with chemogenetically (pharmacologically selective actuator modules, PSAM) or optogenetically (channelrhodopsin 2, ChR2) activated ion channels similarly restores memory deficits. In LgDel+/– animals, therapeutic effects of PVI PSAM-activation are comparable with D2R antagonism [54]. Similarly, ChR2-mediated PVI-activation restores CFC performance in the **5 x familial Alzheimer's disease (5XFAD) model** of AD [58]. Particularly effective in treating animal models of both diseases is PVI ChR2-activation repeated specifically at 40 Hz, mimicking the induction of gamma oscillations and rescuing deficits in SCZ [59,60] and AD models [61,62]. Crucially, imposing oscillations via ChR2 can compensate molecular disruptions of PVI plasticity in supporting memory formation, as demonstrated in γ-CaMKII-deficient mice [63]. This finding in particular highlights the therapeutic potential of engaging PVIs in states of rhythmic activation.

Therefore, by engaging neuromodulation or network synchrony via PVIs, memory deficits in animal models of AD and SCZ can be effectively treated. Particularly based on the finding that the plasticity of network oscillations obeys PVI-dependent DREADD-signaling [3,46,47], we argue that these interventions inherently enable PVI cell-to-network plasticity as the mediator of memory acquisition and consolidation. However, genetic tools remain unavailable to human subjects, motivating the exploration of alternative approaches to target PVI cell-to-network plasticity in the following section.

Molecular targets of PVI cell-to-network plasticity

Candidate targets of PVI cell-to-network plasticity must be both reasonably specific towards PVIs and represent pharmacologically available structures. In the following subsections we summarize evidence implicating mGluR5 and PVI-targeting neuropeptides as promising molecular targets for engaging PVI plasticity (Figure 3) which already demonstrate preclinical efficacy.

mGluR5

SCZ patients exhibit mGluR5 hypofunction [64]; in mice, the cell-type-specific ablation of mGluR5 in PVIs is sufficient to induce core features of neuropsychiatric disease [43]. Recruiting mGluR5 function is therefore an obvious choice of target in treating SCZ. However, direct pharmacological activation of mGluR5 is difficult to control, as the ensuing global increase in excitability renders neurons prone to cell death (reviewed as early as [65]). Rather than direct activation, increasing mGluR5 sensitivity with positive allosteric modulators (PAMs), such as CDPPB [3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide], has proved promising in treating SCZ animal models. However, a certain component of excitotoxicity is retained at higher doses of CDPPB administration due to an augmented recruitment of NMDARs independent of Gq activation [66]. **Biased mGluR5 PAMs** (i.e., VU0409551 and VU0360172) selectively enhance the Gq-component of mGluR5 responsiveness and avoid NMDAR-mediated excitotoxicity [66]. This approach is particularly suited to target PVI plasticity, which requires mGluR5 activation in facilitating PVI-LTP [22,23] and raising the intrinsic excitability of PVIs [25], but is independent of NMDAR activation [20]. In line with this, VU0409551 retains the procognitive and antipsychotic effects of CDPPB and rescues deficits in *ex vivo* gamma oscillations in brain slices of chronically PCP-treated rats [67]. This suggests an underlying link to PVI cell-to-network plasticity, motivating further experimental testing, but already promising clinical efficacy.

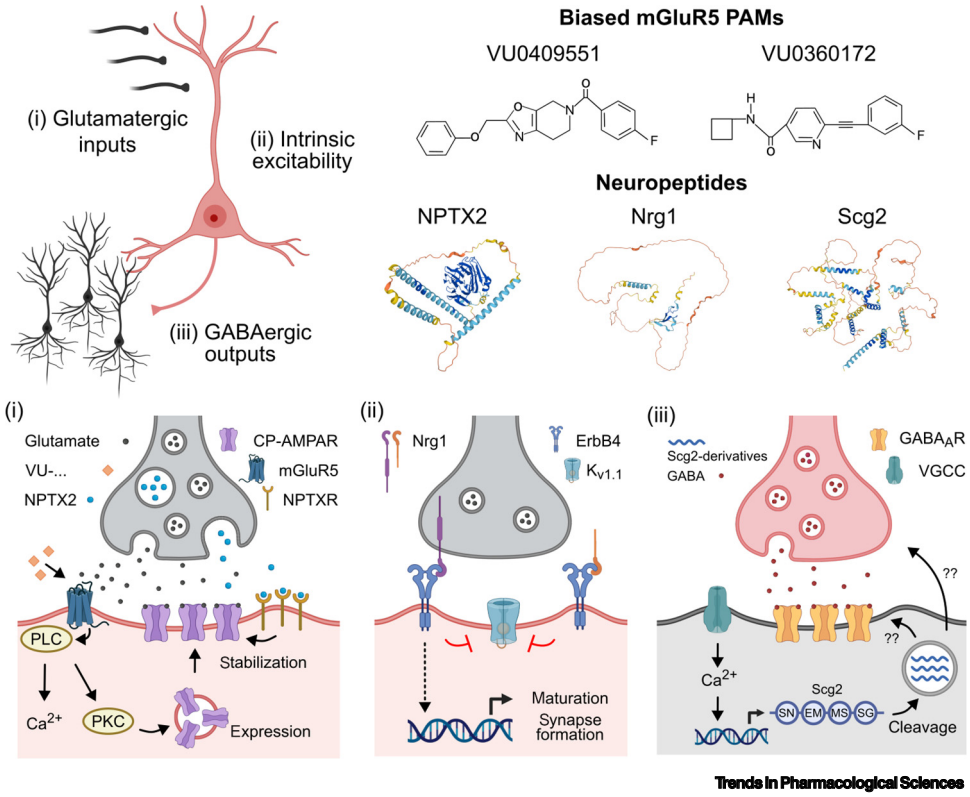

Figure 3. Targeting molecular components of parvalbumin interneuron (PVI) plasticity. Top left: schematic of PVI pharmacological target sites. Top right: pharmacological agents putatively targeting PVI plasticity selectively. Chemical structures for VU0409551 and VU0360172, which selectively target metabotropic glutamate receptor 5 (mGluR5) activation. Tertiary reconstructions of the neuropeptides neuronal pentraxin 2 (NPTX2), neuregulin 1 (Nrg1), and secretogranin 2 (Scg2) taken from AlphaFold [122]. Bottom: putative sites of action for the selected compounds to target PVI plasticity at the glutamatergic input synapse (i), PVI intrinsic excitability (ii), or the GABAergic output synapse (iii). (i) Upon presynaptic activation, glutamate and NPTX2 are released from vesicular stores and activate calcium permeable (CP)-AMPARs (glutamate), mGluR5 (glutamate), and the neuronal pentraxin receptor (NPTX2). VU0409551 or VU0360172 (VU-…) boost the canonical Gq-pathway of PVI-long-term potentiation (LTP), leading to an increased surface expression of CP-AMPARs. Upon binding, NPTX2/NPTXR complexes migrate towards CP-AMPAR sites and stabilize them in the postsynaptic membrane. (ii) Nrg1, both membrane-bound (purple) and soluble (orange), binds to its receptor ErbB4. Acutely, PVIs are rendered more excitable by blockade of the voltage-gated potassium channel Kv1.1. In the long-term, ErbB4 activation supports the transcriptional maturation of PVI as well as successful synapse formation. (iii) Upon coincident postsynaptic pyramidal cell (black membrane) and presynaptic PVI activity, Scg2 is transcribed postsynaptically and promptly cleaved into its constituents: secretoneurin (SN), EM66 (EM), manserin (MS), and Sg2 (SG). By an as yet undisclosed pathway, Scg2 derivatives increase GABAergic transmission either at the pre- or postsynapse. Abbreviations: PAMs, positive allosteric modulators; PKC, protein kinase C; PLC, phospholipase C; VGCC, voltage-gated calcium channel. Images created with BioRender.

Neuropeptides

Neuropeptide-based treatments already display clinical promise in the treatment of neuropsychiatric diseases. For example, intranasal administration of oxytocin improves social abilities in patients with autism spectrum disorder and enduringly stimulates the brain's oxytocinergic system, promising long-term efficacy [68]. Autism is itself linked to PVI dysfunction, and, intriguingly, oxytocin increases neuronal excitability, including in PVIs [69,70]. This has piqued interest in whether oxytocin may alleviate memory deficits in AD [71] and SCZ [72], with promising preclinical results in AD [73,74] but mediocre success in human trials with SCZ patients [75]. Therefore, peptidergic pathways more specific to targeting PVI plasticity may be better suited to target memory deficits in AD and SCZ.

Three peptide classes have recently emerged distinctly relevant to PVI plasticity and network functions in health and disease: neuronal pentraxin 2 (NPTX2), neuregulin 1 (Nrg1), and the precursor molecule Scg2, which preferably target different aspects of PVI plasticity. Whereas NPTX2 stabilizes CP-AMPAR formation at glutamatergic PVI input synapses [76], Scg2 mediates LTP at the GABAergic output synapse by an as yet unknown mechanism [27]. Nrg1, upon activation of the interneuron-specific ErbB4 receptor, primarily affects the intrinsic excitability of PVIs [77]. Despite these differences, their downstream effects converge on the facilitation of gamma oscillations: Nrg1-ErbB4 signaling acutely enhances gamma activity [78] and supports the coherent synchronization of hippocampal and PFC oscillations during higher-order attentional tasks [79]. Ablation of NPTX2 affects hippocampal oscillations upon challenges to the network, for example, epileptic kindling (triggering seizures [80]) or social isolation (reducing gamma oscillation power [81]). Disrupting Scg2 expression in pyramidal cells decreases gamma power and disrupts phase-locking of ensemble neurons [27].

NPTX2, Nrg1, and Scg2 have all been implicated in the pathophysiology of AD and/or SCZ. Ablation of ErbB4 in PVIs is sufficient to induce core features of neuropsychiatric disease [55]. Conversely, administration of Nrg1 elevates PVI excitability and alleviates deficiencies in network oscillations and memory performance in LgDel+/– animals [56]. Nrg1 levels are reduced in SCZ patient plasma during first-episode psychosis and increase upon successful treatment with antipsychotics [82], linking Nrg1 availability and disease severity. NPTX2 levels are decreased in cerebrospinal fluid (CSF) of SCZ [81] and AD patients [83–85]. In animal models of AD, upregulation of NPTX2 exerts neuroprotective effects [86], whereas downregulation renders AD-mutant animals more vulnerable and correlates with cognitive performance and neurodegeneration in human AD patients [83,84]. Scg2 is reduced in the CSF of AD patients [84,85].

Open questions remain regarding the pharmacodynamics of neuropeptide-based interventions [87] and the specificity of targeting widely expressed GPCRs such as mGluR5 [88]. Despite their functioning in supporting memory processes, inadequate activation of mGluR5 [89] or ErbB4 [90] by Aβ oligomers may accelerate neurodegeneration in AD. Finally, the target structures suggested herein rely upon their physiological recruitment during enhanced network activity, which is disrupted in AD and SCZ. Integrating these molecular approaches with strategies harnessing neuronal activity, as discussed in the following section, may support their efficacy.

Gamma frequency stimulation as a clinically viable approach to reinstate memory processes

PVI cell-to-network plasticity is a bidirectional process in which the cellular aspect of plasticity is induced by synchronous network activity. In line with this, two noninvasive approaches imposing network activities at gamma frequencies have gained clinical application and show promise in the treatment of AD and SCZ (Figure 4A).

The first approach enforces membrane oscillations via electrical field fluctuations. **Repetitive transcranial magnetic stimulation (rTMS)** or **transcranial electric stimulation (tES)** are focally applied to activate local neuronal populations at a predefined rate. The physical interventions underlying these approaches affect the manner in which neurons are recruited [91–94]. rTMS directly activates neurons by depolarizing pyramidal neuron processes, initiating a local burst of activity and synchronizing firing rates upon repetitive stimulation. Electrical fields generated by tES are by comparison weaker and insufficient to generate action potentials. Instead, neurons are briefly rendered either more excitable or less (transcranial direct current stimulation, tDCS) or coerced to phase-lock in the given rhythm (transcranial alternating current stimulation, tACS). In all cases, transcranial stimulation purportedly supports the induction of synaptic plasticity within

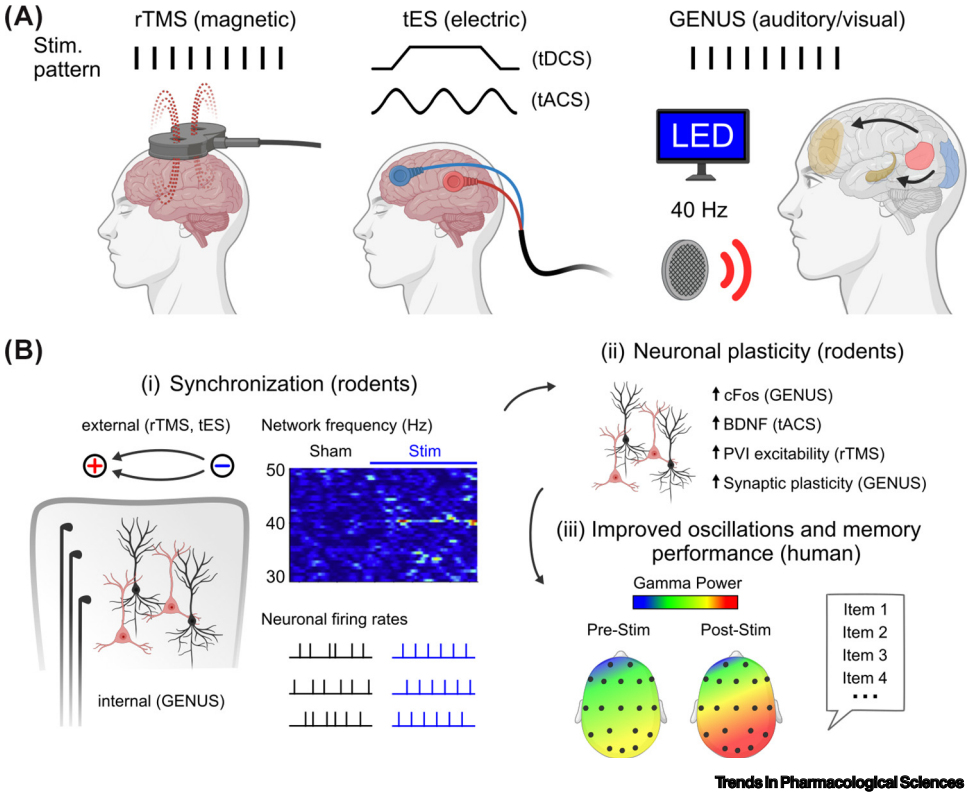

Figure 4. Stimulation-based approaches in the treatment of neuropsychiatric disorders. (A) Illustrations of clinically available, noninvasive interventions stimulating brain activity. Stimulation patterns for repetitive transcranial magnetic stimulation (rTMS) and gamma entrainment using unspecific sensory stimuli (GENUS) are discontinuous, transcranial electrical stimulation (tES) includes continuous direct (tDCS) or alternating current stimulation (tACS). Visual and/or auditory cues for GENUS are applied at 40 Hz and recruit the primary visual (blue shaded area) or auditory cortex (red shaded area), which subsequently entrain the hippocampus and prefrontal cortex (yellow shaded areas). (B) A framework of cell-to-network plasticity underlying the clinical efficacy of stimulation-based treatments. (i) Left: stimulation-based interventions recruit local cortical microcircuits either by imposing external extracellular currents (rTMS, tES) or by recruiting upstream structures (black synapses, GENUS). Right: exemplary pseudocolor plot from a local field potential recording during visual GENUS in mouse prefrontal cortex (image adapted from [100]). Upon stimulation, a persistent 40 Hz signal is detected. During GENUS, firing rates of local neurons are preferentially phase-locked to the imposed rhythm. (ii) Following stimulation, local neuron populations – including pyramidal neurons (black) and parvalbumin interneurons (PVIs) (red) exhibit different markers of neuronal plasticity, including increased expression of the immediate early gene cFos and brain-derived neurotrophic factor (BDNF). (iii) Stimulation-induced neuronal plasticity is reflected by increased gamma oscillation power in electroencephalogram (EEG) recordings and accompanied by improved recall in verbal memory tasks. EEG pseudocolor maps adapted from [109] demonstrating 40 Hz tACS improves gamma power and verbal memory in patients with Alzheimer's disease. Images created with BioRender.

minutes following stimulation, with a special focus in recent years on stimulation frequencies mirroring theta rhythms (5–10 Hz) and gamma rhythms (30–50 Hz) [91,92,94]. Current clinical applications include post-stroke motor function recovery, treatment-resistant depression, and obsessive–compulsive disorder, yet ongoing clinical trials expand their application to SCZ and AD. Most commonly, the dorsolateral PFC and the temporal lobe (containing the hippocampus) are targeted as stimulation sites, in line with their purported functions in memory generation. Recent meta-analyses reveal both antipsychotic effects and improved cognitive functions effective within a range of weeks yet suffer from inconsistent population samples and study designs [95–99].

Gamma entrainment using unspecific sensory stimuli (GENUS) represents a more physiological approach driving local network oscillations. Rhythmic presentation of sensory stimuli

specifically at 40 Hz evokes corresponding neuronal oscillations in primary cortices, which synchronize their downstream, associative targets, the hippocampus and the PFC [100]. GENUS therefore makes use of the existing neuronal connectivity to recruit local networks in concert with their functional partners at distant sites. Further, application of GENUS perpetuates neuroprotective measures of non-neuronal origin, including microglia and astrocyte activation, increased cerebrovascular perfusion and glymphatic clearance [101,102]. This approach ameliorates disease pathology in AD, reducing plaque density and conserving memory performance up to weeks following stimulation in both rodents and humans (most recently reviewed in [96]). Importantly, effects of GENUS are modulated by attentional state: GENUS entrainment of temporal regions is enhanced in humans when subjects perform a concurrent attention task [103], yet failed in a rodent study in which animals responded aversively to stimulation with no subsequent plaque reduction [104]. Beyond its application in AD, animal studies suggest promise in the treatment of SCZ, indicating a more general pro-cognitive function rescuing memory deficits [105,106].

It is enticing to associate the mechanistic approach of transcranial or sensory stimulation to mechanisms governing PVI cell-to-network plasticity. In animals, GENUS mimics optogenetic PVI stimulation, and its dependency on intact GABAergic transmission indicates a prerequisite for PVI activation, which is mirrored by increased expression of the immediate early gene cFos in PVIs [61,105]. Similarly, rTMS enhances PVI excitability during critical period plasticity in the visual cortex [107], and tACS preferentially recruits PVIs to phase-lock to the applied current [108]. Finally, preliminary results suggest that tACS and/or rTMS applied at gamma frequencies increase subsequent gamma oscillations in AD patients and healthy subjects [109–111]. Given the cumulative evidence tying gamma frequency stimulation to PVI plasticity and both to memory processes, it is reasonable to assume that these strategies exert their therapeutic effect on memory performance via enhanced PVI recruitment (Figure 4B).

It is important to note, however, that current clinical data do not allow direct conclusions about whether and to what extent PVI plasticity is induced in human patients following gamma frequency stimulation. Inter-study stimulation paradigms are heterogeneous regarding the duration and site of stimulation as well as subsequent clinical evaluation, complicating any mechanistic analyses. Further, direct assessments of PVI plasticity as obtained from animals (e.g., expression of parvalbumin or PNNs, electrophysiological recordings) are currently unavailable in humans, as they require invasive measures. Therefore, adapting study protocols to allow for reproducible, non-invasive quantifications of PVI cell-to-network plasticity presents a major task for future research.

Concluding remarks and future perspectives

PVI cell-to-network plasticity controls the emergence of memory processes, dysfunctions of which represent a major untreated symptom in AD and SCZ. Here, we propose that addressing its interaction sites represents a promising approach to reinstate memory processes, and we argue that novel, stimulation-based treatments of these diseases already make use thereof. Importantly, the conclusions offered here do not preclude the putative efficacy of other novel treatment avenues. On the contrary, it is possible that strategies targeting neuronal regeneration [16] or GABAergic transmission [17] may similarly converge on the reinstatement of intact neuronal oscillations, setting the stage for functional PVI plasticity. For the time being, the precise mechanisms by which successful preclinical interventions rescue memory deficits remain to be determined (see Outstanding questions).

If rTMS, tES, and GENUS target PVI plasticity by imposing network oscillations, what need is there for additional, cell-type-specific interventions? Whereas present clinical data suggest that gamma stimulation alleviates memory deficits, resulting memory function most likely remains inferior to healthy subjects or solely prevents further decline. A possible explanation lies in the

Outstanding questions

To what extent do PVI cell-to-network plasticity rules as laid out here apply to the human cortex?

Do preclinically effective, PVI-specific neuropeptides (NPTX2, Nrg1, Scg2-derived peptides) exert a pro-cognitive effect in human AD and/or SCZ patients?

Are intranasal administration strategies, as applicable for oxytocin, also available for PVI-specific neuropeptides?

In the case of a preclinically promising candidate neuropeptide, can this be tailored to act in specific cortical regions (PFC, hippocampus), for example, upon transcranial stimulation?

Are the positive effects of gamma stimulation strategies (rTMS, tES, GENUS) on memory performance at least in part mediated by inducing PVI cell-to-network plasticity?

Can PVI cell-to-network plasticity be clinically assessed as a cell-type-specific contribution to overall memory function? Crucially, can this be achieved noninvasively: for example, by plasticity-centered EEG/MEG recordings or serum-based parameters indicating the state of PVI function?

activity-dependent, cellular side of PVI plasticity: if PVI functions are disrupted, as in AD and SCZ, their plasticity mechanisms are less likely to be engaged. This includes disruptions of mGluR5 or ErbB4 signaling, a lack of available PVI-specific neuropeptides, or reduced parvalbumin expression. Lowering the induction threshold of PVI plasticity by supporting these pathways may maximize the effects of concurrent gamma stimulation and possibly restore memory deficits to prior capabilities. Harnessing the therapeutic potential of PVI cell-to-network plasticity, however, entails probing a large parameter space of available stimulation paradigms and molecular targets, which may interact differently depending on the underlying pathology. Establishing optimal stimulation conditions will require a high standardization of assessing PVI plasticity in the human brain and clinical consensus on how to quantify pro-cognitive efficacy as the final patient outcome.

Accepting the aforementioned assumptions, clinicians face the question of whether PVI plasticity can be assessed as a biomarker for therapy success. Toward this, auditory steady-state responses (ASSRs) have proved a consistent biomarker for disease state in SCZ [13] and correlate with cognitive performance in AD patients [112]. Mimicking auditory GENUS on a shorter time scale, 40 Hz presentation of auditory stimuli induces robust oscillatory activity in electroencephalography/magnetoencephalography (EEG/MEG) recordings, with ASSR power deficits apparent in SCZ high-risk patient cohorts before symptom onset. Adjusting such a protocol to account for memory-task-induced changes in gamma power may serve as an ad hoc, noninvasive estimate of the capacity for PVI plasticity. Other aspects of PVI plasticity, such as PV expression state or the distribution of PNNs, currently remain unavailable to clinicians. However, given advances in examining CSF or blood plasma levels of disease markers in AD and SCZ [82,84,85], by-products of parvalbumin or PNN metabolism may emerge as additional markers of PVI plasticity state.

Finally, the mechanistic reasoning and molecular strategies proposed here rely on findings in rodents. Analyses of human brain tissue reveal a higher diversity of interneurons in general and PVI subclasses in particular [113]. Further, the cortical expansion of the human brain challenges PVI synaptic functions, to which they adapt on an anatomical and electrophysiological level [114,115] and may translate to mechanisms underlying PVI plasticity, neuronal oscillations, and memory formation. Intensifying efforts to explore the interactions between cellular and network levels in the human brain may not only help to establish the feasibility of future cell-type-specific interventions in AD and SCZ, but rather open new avenues targeting previously unknown mechanisms of PVI plasticity.

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Author contributions

M.D.H. conceived and wrote the initial manuscript draft and created the figures. All authors contributed to the final manuscript.

Declarations of interests

The authors declare no conflicts of interests.

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