Translation-Focused Approaches to GPCR Drug Discovery for Cognitive Impairments Associated with Schizophrenia

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ABSTRACT: There are no effective therapeutics for cognitive impairments associated with schizophrenia (CIAS), which includes deficits in executive functions (working memory and cognitive flexibility) and episodic memory. Compounds that have entered clinical trials are inadequate in terms of efficacy and/or tolerability, highlighting a clear translational bottleneck and a need for a cohesive preclinical drug development strategy. In this review we propose hippocampal–prefrontal–cortical (HPC–PFC) circuitry underlying CIAS-relevant cognitive processes across mammalian species as a target source to guide the translation-focused discovery and development of novel, procognitive agents. We highlight several G protein-coupled receptors (GPCRs) enriched within HPC–PFC circuitry as therapeutic targets of interest, including noncanonical approaches (biased agonism and allosteric modulation) to conventional clinical targets, such as dopamine and muscarinic acetylcholine receptors, along with prospective novel targets, including the orphan receptors GPR52 and GPR139. We also describe the translational limitations of popular preclinical cognition tests and suggest touchscreen-based assays that probe cognitive functions reliant on HPC–PFC circuitry and reflect tests used in the clinic, as tests of greater translational relevance. Combining pharmacological and behavioral testing strategies based in HPC–PFC circuit function creates a cohesive, translation-focused approach to preclinical drug development that may improve the translational bottleneck currently hindering the development of treatments for CIAS.

KEYWORDS: schizophrenia, cognitive impairment, hippocampal–prefrontal cortical circuitry, preclinical, drug discovery, GPCRs, rodent touchscreen

1. INTRODUCTION

Schizophrenia is a complex neuropsychiatric disorder that affects around 0.3% of the population¹ and remains among the leading causes of disability worldwide.² Schizophrenia symptoms are highly heterogeneous, with positive and negative symptoms making up the core diagnostic criteria,³ but these clinical features are frequently preceded by cognitive dysfunction.^{4,5} Cognitive impairments associated with schizophrenia (CIAS) are highly detrimental to functional capacity,^{6–8} and the severity of CIAS is the most accurate predictor of patient outcomes.^{9–12} As such, cognitive deficits are becoming increasingly accepted as a core feature of schizophrenia and not just an epiphenomenon, with many clinical professionals advocating for their inclusion in diagnostic criteria.^{13–16}

The cognitive domains most consistently dysfunctional in schizophrenia, as highlighted by the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) and Measurement and Treatment Research to

Improve Cognition in Schizophrenia (MATRICS) initiatives, include working memory, attention, cognitive flexibility, and episodic memory.^{17,18} The extent of dysfunction in these domains is typically classified as “moderately severe” to “severe” with patients performing 1.5–2.5 standard deviations below neurotypical controls.^{16,19,20} Furthermore, these deficits present in around 85% of schizophrenia cases²¹ and persist while worsening throughout the patient’s lifetime.^{22–24}

Over the last 60 years of drug development, there has been a disproportionate prioritization of antipsychotic therapeutics targeting the positive symptoms, over the development of procognitive agents. Prior to the development of the

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MATRICES initiative in 2004, which defined how CIAS should be assessed and treated, the Food and Drug Administration (FDA) would only approve drugs for schizophrenia if they reduced positive symptoms.^{25–27} To date, no antipsychotic drug meaningfully improves cognition in patients with CIAS,^{28–35} and procognitive treatments for indications such as Alzheimer's disease have no efficacy for CIAS.^{36–38} Despite the MATRICES initiative, the lack of therapeutic options available to patients highlights the depth of the translational bottleneck.^{39,40} There is an urgent need for a cohesive, translation-focused preclinical strategy for the design and testing of putative procognitive agents for CIAS.

This review discusses how the growing understanding of circuitry underlying CIAS offers a source of innovation for the discovery of novel, procognitive agents with high translational relevance. We review the hippocampal–prefrontal cortical (HPC–PFC) circuits implicated in the cognitive processes most consistently dysfunctional in CIAS (working memory, cognitive flexibility, and episodic memory; section 2), highlighting the conservation of these mechanisms across mammalian species. We then consider how this knowledge facilitates the identification of novel, HPC–PFC circuit-enriched G protein-coupled receptor (GPCR) targets (section 3), which allow for more nuanced and selective control over specific circuits than other targets. Finally, we highlight how the validation of prospective procognitive agents can be accelerated by improved preclinical cognition tests with greater potential for successful translation into the clinic (section 4). Collectively, we suggest a cohesive, translation-focused approach to preclinical drug discovery that may improve the translational bottleneck currently hindering the development of effective treatments for CIAS.

2. HPC–PFC CIRCUITRY IN CORE COGNITIVE DOMAINS RELEVANT TO CIAS

The last two decades have seen a more fundamental biological approach to diagnosing, understanding, and treating mental illnesses. Primarily, this has been to assess observable behaviors as caused by neurocircuitry and neurochemistry rather than predefined symptom presentation.^{41,42} The development of methods allowing for the quantification of interactions between brain regions such as electrophysiology, electroencephalography (EEG), and functional neuroimaging have been crucial in providing detailed insight into specific neurocircuit processes implicated in CIAS.⁴³ Aberrant neurocircuit function underlies several hypotheses for CIAS pathology, such as the disconnection hypothesis⁴⁴ and the excitation/inhibition imbalance hypothesis.^{45,46} These neurocircuit-based hypotheses suggest that impaired functional and anatomical connections in and between key brain regions drive many schizophrenia-relevant neural dysfunctions with cognitive consequences, i.e., in synaptic plasticity and neural synchrony.

The hippocampus (HPC), prefrontal cortex (PFC), and their associated circuits are consistently implicated in cognitive processes relevant to CIAS across mammalian species.^{47–49} Structural and functional abnormalities within HPC–PFC circuitry are observed in schizophrenia patients⁵⁰ and are commonly reflected in various animal models of schizophrenia-relevant symptoms.⁵¹ Herein we detail the specific HPC–PFC circuits critically involved in three cognitive processes commonly dysfunctional in CIAS: working memory, cognitive flexibility, and episodic memory.

2.1. Working Memory. Working memory describes the storage of task-relevant information in the short term to aid in the completion of a task but not to be remembered thereafter. Effective communication between the HPC and PFC is critical for working memory performance in a manner that is remarkably well-conserved across mammalian species. Indeed, the HPC and medial PFC (mPFC) are highly synchronized during spatial working memory performances in humans,^{52–56} rats,^{57,58} and mice.^{59–61} The nucleus reuniens (NRe) of the midline thalamus makes strong, reciprocal, excitatory connections with the mPFC and the dorsal and ventral HPC^{62,63} and contains neurons that project simultaneously to both structures^{64,65} (Figure 1, top).

Figure 1. Schematic representation of the HPC–PFC neurocircuits underlying the key cognitive processes dysfunctional in CIAS. Key excitatory, inhibitory, and disinhibitory projections between the HPC, PFC, NRe, EC, and NAc engaged during working memory, episodic memory, and cognitive flexibility processes. PFC, prefrontal cortex; HPC, hippocampus; NRe, nucleus reuniens; EC, entorhinal cortex; NAc, nucleus accumbens; VTA, ventral tegmental area. Solid arrows, excitatory; blunted arrows, inhibitory; dotted arrows, disinhibitory.

Inactivation studies of the NRe have highlighted its critical role in the functional connectivity of the mPFC and HPC by maintaining synchronous activity during spatial working memory tasks in rodents.^{66–69} Various encephalography and functional imaging techniques have revealed aberrant functional coupling and synchrony between the human dorsolateral PFC (dlPFC; equivalent to the mouse mPFC) and HPC

during working-memory tasks in chronic schizophrenia patients,^{70–74} first-episode patients, at-risk individuals, and first-degree relatives of patients.^{75,76} This highlights the endophenotypic nature of aberrant HPC–PFC circuitry and working memory dysfunction in schizophrenia.^{77,78} Furthermore, various animal models also display impaired HPC–PFC synchrony that correlates with working memory performance.^{79–82}

2.2. Cognitive Flexibility. Cognitive flexibility comprises multiple executive functions that allow shifting between multiple tasks, perspectives, or strategies, ultimately to update goal-directed behavior. It includes the ability to refocus attention to update rules on relevant versus irrelevant stimuli (attentional set-shifting), and the ability to update new feedback on action–outcome contingencies within a context to adapt behavioral responding to be more optimal (behavioral flexibility).^{83,84} Given the high level of cognitive control, cognitive flexibility has been shown to require complex neural networks involving multiple brain regions (Figure 1, middle). When carrying out functions that require cognitive flexibility such as during goal-directed behavior, the nucleus accumbens (NAc) of the ventral striatum is proposed to integrate information from limbic and cortical regions into behavioral outcomes via the ventral tegmental area (VTA).^{85–87}

Intact and functional connectivity of HPC–NAc–VTA–PFC circuitry is critically involved in goal-directed behaviors and executive functions in humans,^{88–90} nonhuman primates,⁹¹ and rodents.^{85,92–94} Furthermore, in addition to its role in spatial working memory, rodent studies have implicated the PFC–NRe–HPC circuit in cognitive flexibility functions such as attentional set-shifting and reversal learning (RL).^{95–99} Indeed, large-scale networks involving the PFC, HPC, thalamus, striatum, and other limbic structures such as the amygdala are frequently implicated in executive processes and goal-directed behaviors.^{100–103} Functional neuroimaging studies involving patients with CIAS show impaired connectivity between, and engagement of, the PFC, HPC, NAc, and thalamus during behaviors requiring cognitive flexibility,^{104–106} and several animal models commonly used to represent CIAS consistently display deficits in similar cognitive flexibility behavioral paradigms.^{107–113}

2.3. Episodic Memory Encoding and Retrieval. Episodic memory describes the long-term storage of memories containing information pertaining to the ‘what, where, and when’ of autobiographical events. While animals cannot speak about their past experiences, they are able to learn behavioral tasks that rely on episodic or episodic-like memory, typically involving remembering a particular item (“what”) in a particular context (“where”).^{114–116} The entorhinal cortex (EC) is considered the hub for the cortical–hippocampal episodic memory network as it receives dense excitatory input from several cortical areas including the PFC, perirhinal cortex (PC), and parahippocampal cortex (PHC) and relays this cortical information directly to the HPC via disinhibition during episodic memory encoding.^{117–119} The HPC sends projections back to cortical areas forming a functional feedback “loop”, allowing the HPC to retrieve contextual information via the EC during memory retrieval that has been integrated initially by the PFC.^{120,121} (Figure 1, bottom).

Disconnection studies of PFC–HPC and PFC–EC connectivity produce significant deficits in episodic memory encoding and retrieval in rodents,^{122–124} while neuroimaging and lesion studies in humans consistently implicate con-

nectivity between PFC and medial temporal lobe structures (HPC, EC, PC, and PHC) during episodic encoding and retrieval.^{125–127} Functional neuroimaging studies further show a reduced ability for patients with CIAS to engage the dorsolateral PFC, HPC, and other cortical and medial temporal lobe structures during episodic memory tasks.^{128–130} Furthermore, commonly used animal models of CIAS produce deficits in episodic memory tasks^{131,132} along with thinning of the EC,¹³³ reflecting the neuropathological characteristics seen in schizophrenia patients, antipsychotic-treatment-naïve or otherwise.^{134,135}

3. HPC–PFC CIRCUIT-ENRICHED GPCR TARGETS FOR THE TREATMENT OF CIAS

3.1. GPCRs as Neurotherapeutic Targets. G protein-coupled receptors (GPCRs) constitute the largest family of cell surface receptors and are the target for the greatest proportion of currently marketed therapeutics (~34%).^{136–139} They mediate signaling by ligands as diverse as protons, amino acids, biogenic amines, peptides, and proteins. While the topic is too complex to cover in any depth herein, heterotrimeric G proteins of different families transduce these extracellular stimuli into excitatory or inhibitory intracellular second messenger cascades,¹⁴⁰ primarily modulating levels of cyclic nucleotides, inositol phosphates, and intracellular calcium. Another dimension of GPCR signaling emerged when it was shown that β -arrestin proteins, far from simply acting as “signal-terminating” proteins, scaffold their own signaling to downstream effectors, such as ERK1/2 (extracellular signal-regulated kinase 1/2). Irrespective of its dependence on G proteins and/or β -arrestins, metabotropic signaling shapes the responses elicited by fast ionotropic synaptic transmission, including modulating synaptic plasticity, which drives learning, memory, and attention.¹⁴¹ While ionotropic receptors such as N-methyl-D-aspartate (NMDA; GluN),¹⁴² α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA; GluA),¹⁴³ γ -aminobutyric acid type A (GABA_A),¹⁴⁴ and α 7 nicotinic receptors¹⁴⁵ have been implicated in schizophrenia pathophysiology and as direct and indirect drug targets, these approaches are beyond the scope of this review. Rather, given the general tractability of GPCRs to drug discovery, contemporary approaches available to selective targeting of members of this superfamily (*vide infra*) and specific localization of some GPCRs in relevant HPC–PFC circuitry (Figure 2), we focus on opportunities for novel GPCR-targeted CIAS drug discovery.

Several GPCRs, including the dopamine D₁ and D₂, muscarinic M₁, serotonin 5-HT₆, and histamine H₃ receptors are enriched in HPC–PFC circuitry in mice and humans. Compounds targeting these receptors have met with varying degrees of success in clinical trials, but none has yet resulted in an approved therapeutic for CIAS. While this has often been due to lack of efficacy, e.g., H₃ antagonists, other limitations have been insufficient subtype selectivity or target-mediated side-effects, e.g., dopamine D₁ and muscarinic M₁ agonists, *vide infra*.

Many of these limitations of “old targets” could be addressed by harnessing advances in our understanding of GPCR pharmacology. Equally, contemporary drug discovery methods may also provide a path for “new targets”, such as orphan GPCRs, which have emerged from the genomic-era of drug discovery. Incorporating the most appropriate mechanism of

Figure 2. Messenger RNA expression levels of therapeutically relevant GPCRs in key nodes of HPC–PFC circuitry. Therapeutically relevant GPCRs are enriched in key nodes of HPC–PFC circuitry in both mice and humans compared to the putative negative control, *Grm6*. DropViz data are mouse brain single-cell neuronal mRNA expression levels in transcripts per 100 000 unique molecular identifiers; each data point represents expression level in a genetically defined neuronal population (where there are fewer data points it is due to lack of expression in certain neuronal populations).³¹⁷ Janelia data are from NeuroSeq mouse brain initiative and represent single-cell neuronal mRNA expression levels in transcripts per million; each data point represents expression level in a genetically distinct neuronal population (where there are fewer data points it is due to lack of expression in certain neuronal populations).³¹⁸ HPA data are regional human brain mRNA expression data combined from Consensus Human Brain (normalized), GTEx Human Brain mRNA (transcripts per million), and the FANTOM Human Brain CAGE (scaled tags per million) data sets as follows:^{319,320} CTX, cortex, includes frontal cortex (DropViz); insula, ectorhinal, orbital, primary motor, somatosensory, retrosplenial, visual, and isocortex (NeuroSeq/Janelia); cerebral cortex, BA24, BA9, frontal lobe, insula, medial frontal gyrus, medial temporal gyrus, occipital, parietal lobe, and temporal lobe (CHB/GTEX/FANTOM CAGE); HPC, hippocampus, includes hippocampus (DropViz); CA1, CA2, CA3, dentate gyrus, and subiculum (NeuroSeq/Janelia); hippocampal formation (CHB/GTEX/FANTOM CAGE); Thal, thalamus, includes thalamus (DropViz); anterodorsal nucleus, anteroventral nucleus, central lateral nucleus, lateral geniculate complex, paracentral nucleus, paraventricular nucleus, and ventral posteromedial nucleus (NeuroSeq/Janelia); thalamus (CHB/GTEX/FANTOM CAGE). *Drd1*, dopamine D₁ receptor; *Drd2*, dopamine D₂ receptor; *Chrm1*, M₁ muscarinic acetylcholine receptor; *Htr6*, serotonin 5-HT₆ receptor; *Hrh3*, histamine H₃ receptor; *Gpr52*, orphan GPR52; *Gpr139*, orphan GPR139; *Grm6*, mGlu₆ metabotropic glutamate receptor. Vertical lines indicate the mean of the data set (including zero values not shown on Log₂ axis; n/a = not available in the database).

action for a drug in the context of a given disease state is critical to its chances of success.

Two approaches that are revolutionizing the field of small-molecule drug discovery are “allosteric modulation” and “biased agonism”. Allosteric modulators (Figure 3) bind to secondary sites on receptor proteins that are distinct from, but conformationally linked to, the endogenous ligand binding site (“orthosteric site”; Figure 3). These sites open up new avenues for medicinal chemistry and greater receptor-subtype-selectivity. Allosteric modulators either enhance or diminish the

responses to the endogenous agonist, effectively acting as a “dimmer switch” mechanism.¹⁴⁶ In contrast to orthosteric agonists and antagonists, allosteric modulators preserve the spatial and temporal nature of endogenous signaling,^{146–148} which is important for complex cognitive processes that rely on conservation of the dynamics of neurotransmission. Further control is engendered by the cooperativity between an allosteric modulator and the endogenous agonist. This governs the direction and magnitude of the modulation, providing a ceiling level to the effect, which can be designed to align with

Figure 3. Modalities of targeting GPCRs in drug discovery. (A) Classical targeting: Classical modes of drug action at GPCRs involve engaging the same site as the endogenous ligand (the orthosteric binding site), either directly activating the receptor (agonist) or preventing the actions of the endogenous ligand (antagonist). (B) Allosteric modulation: Allosteric modulators bind to secondary sites distinct from, but conformationally linked to, the orthosteric binding site, to modulate endogenous agonist affinity and/or efficacy. Most commonly, a negative allosteric modulator (NAM) will reduce the intracellular signal of the endogenous agonist while a positive allosteric modulator (PAM) will enhance its signal. (C) Biased agonism: Biased agonists trigger specific intracellular signaling cascades to a greater extent than others, even when different levels of stimulus–response coupling for pathways are taken into account. In this example, the endogenous ligand (left) signals pathway #3 > pathway #2 > pathway #1, whereas a biased agonist (right) differentially activates the same subset of pathways.

the desired therapeutic outcome while avoiding on-target effects associated with overstimulation or complete inactivation of a receptor.

The second novel paradigm for targeting GPCRs is through “biased agonists” (Figure 3), which trigger specific intracellular

signaling cascades at the relative or total exclusion of others, thereby enabling the activation of therapeutically relevant cellular responses while avoiding those linked to on-target adverse effects.^{149,150} Many biased agonists grossly discern G protein versus β -arrestin mediated signaling,¹⁵¹ and theoretically, it is also possible to combine the two phenomena. Allosteric modulators can differentially promote or inhibit the signaling of agonists to particular signaling pathways.¹⁵²

Applying these alternative targeting modalities to GPCR drug discovery for CIAS represents an opportunity for a new generation of therapeutic agents capable of selectively modulating key circuitry. Key GPCR approaches to CIAS are summarized below and in Table 1.

3.3. Mechanisms of Action of Putative Therapeutic Agents for CIAS. 3.3.1. Dopamine D₁ Receptor Agonists/PAMs.

The dopamine D₁ receptor is the most highly expressed dopamine receptor subtype in the PFC¹⁵³ and has been consistently implicated in cognitive functions relying on PFC function such as attention, working memory, and other executive processes.¹⁵⁴ Importantly, its function in the PFC yields an inverted U-shape relationship such that too much or too little activation is detrimental to cognitive outcome.^{155–157}

Unfortunately dopamine D₁ receptor agonists have notoriously poor tolerability and pharmacokinetics, tachyphylaxis, and severe adverse effects in clinical trials.^{158–160} Dihydroxylidone, a centrally acting, selective dopamine D₁ receptor full agonist,¹⁶¹ improved working memory deficits in patients with schizotypal personality disorder,¹⁶² but it caused mild to moderate cardiovascular side-effects that prevented its further development.

The selective, noncatechol dopamine D₁/D₅ receptor partial agonist PF-06412562 was developed to avoid such bioavailability and safety concerns. Originally trialed as an efficacious anti-Parkinsonian agent with few cardiovascular side-effects,¹⁶³ PF-06412562 was recently found to be safe and well-tolerated in a phase Ib clinical trial for schizophrenia.¹⁶⁴ Unfortunately, it failed to display procognitive efficacy, which the study authors attributed to the conservative, safety-focused study design.

Recently, there has been significant effort to develop noncatechol D₁ receptor positive allosteric modulators^{165,166} (PAMs; Figure 3B) with improved subtype selectivity, a greater therapeutic index, better pharmacokinetics, and a lack of tachyphylaxis by not constantly activating the receptor.¹⁶⁷ The dopamine D₁ receptor PAM, DETQ reverses episodic-like memory deficits in mouse models of CIAS while enhancing acetylcholine signaling in the PFC and HPC.¹⁶⁸ Astellas Pharma has patented two families of dopamine D₁ receptor PAMs indicated for the treatment of CIAS, Alzheimer’s, Parkinson’s, and Huntington’s diseases,^{169,170} which reverse working memory deficits in mouse models of CIAS. Astellas Pharma also recently sponsored a phase IIa clinical trial to evaluate the safety and procognitive efficacy of ASP4345, as an add-on treatment in 233 patients with CIAS [NCT03557931] after it improved information processing, visual attention, and mismatch negativity in patients with schizophrenia or schizoaffective disorder in a phase Ib trial.¹⁷¹ Disappointingly, Astellas Pharma announced in May 2020 that the program had been discontinued as the primary end point in phase II had not been met;¹⁷² it is not clear whether this represents a limitation of study design, e.g., add-on therapy, inappropriate compound pharmacology/pharmacokinetics, or limitation of the dopamine D₁ receptor as a target *per se*.

Table 1. GPCR-Targeting Compounds Currently (or Recently) in Preclinical and Clinical Development for the Treatment of CIAS^a

mechanism of action	drug/compound	company/institute	phase of development (year)	clinical trial end-points [trial ID]	outcome	ref
dopamine D ₁ agonists/PAMs	dihydroxidine	Antonia New, Icahn School of Medicine at Mount Sinai	II (2018)	attention and working memory performance schizotypal personality disorder [NCT02507206]	improvements in working memory, moderate cardiovascular side-effects	162
	PF-06412562	Pfizer	Ib (2016)	safety, tolerability and working memory performance as an add-on treatment in patients with schizophrenia [NCT02418819]	safe and well-tolerated, no improvements in working memory	164
	ASP4345	Astellas Pharma	Ila (2019)	safety, tolerability and cognitive performance in MCCB as an add-on treatment in patients with schizophrenia [NCT03557931]	unpublished, but project discontinued	172
dopamine D ₂ biased agonists muscarinic M ₁ agonists/PAMs	UNC99 series	University of North Carolina	preclinical		improvements in episodic-like memory deficits in PCP-treated mice (NOR)	190
	xanomeline	Eli Lilly and Company	II (2008)	safety, tolerability, antipsychotic efficacy and performance in a cognitive test battery in patients with schizophrenia	antipsychotic efficacy, improvements in verbal learning and short-term memory, moderate gastrointestinal side-effects	199
	KarXT (xanomeline + trospium)	Karuna Therapeutics	II (2019)	Safety, tolerability and antipsychotic efficacy in patients with schizophrenia [NCT03697252]	unpublished, presumed safe and well-tolerated according to public announcement, no mention of future assessments on cognition	201
serotonin 5-HT ₆ antagonists	GSK1034702	GlaxoSmithKline	Ib (2010)	safety, tolerability and performance in a touchscreen cognitive test battery in nicotine-abstained smokers [NCT01371799]	improvements in model-induced impairments in episodic memory, mild gastrointestinal side-effects	202
	AVN-211	Avineuro Pharmaceuticals	II (2014)	PANSS score and performance in tests of attention as an add-on treatment in patients with schizophrenia	improvements in attention	220
	AVN-322	Avineuro Pharmaceuticals	I (2017)	PK, safety and tolerability in healthy volunteers	good PK, safety and tolerability profile	221
GPR52 agonists	FTBMT/3-BTBZ series	Takeda Pharmaceutical Company	preclinical		improvements in episodic-like memory (NOR) and working memory (RAM) deficits in MK-801-treated rats	226
	unknown GPR52 agonist	Beacon Discovery/Boehringer Ingelheim Pharma	preclinical		improvements in cognitive flexibility (ASST) in PCP-treated rats	230
	HTL-A	Sosei Heptares	preclinical		improvements in cognitive flexibility (RL) in PCP-treated rats	231
GPR139 agonists	TAK-041	Takeda Pharmaceutical Company/Neurocrine Biosciences	II (2019)	performance in the BACS task as an add-on treatment in patients with schizophrenia [NCT03319953]	unpublished	

^aAbbreviations: MCCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery; PCP, phencyclidine; NOR, novel object recognition; PANSS, positive and negative syndrome scale; PK, pharmacokinetics; RAM, radial arm maze; BOLD, blood-oxygen-level-dependent; BACS, Brief Assessment of Cognition in Schizophrenia. Trial IDs are as listed on clinicaltrials.gov.

Despite the above setbacks there are other D₁ receptor partial agonists (tavapadon, phase III [NCT04201093]; CVL-871, phase I) and PAMs (LY3154207, phase II [NCT03305809]) in active development for non-CIAS indications, including dementia and Parkinson's disease. It remains to be seen whether these agents might be successfully repurposed for the treatment of CIAS.

3.3.2. Dopamine D₂ Receptor Biased Agonists. Blockade of dopamine D₂ receptors to counteract aberrantly high dopaminergic tone in the striatum is integral to antipsychotic efficacy.^{173,174} All currently marketed antipsychotic drugs functionally antagonize the dopamine D₂ receptor. However, endogenous activation of hippocampal dopamine D₂ is positively correlated with performances in schizophrenia-related cognitive tasks that rely on functional HPC–PFC circuitry.¹⁷⁵ Furthermore, chronic antipsychotic treatment is associated with progressive cognitive impairment and exacerbation of neuropathological characteristics indicative of schizophrenia in nonhuman primates and lower order species.^{176–178} This presents a problem whereby to achieve simultaneous antipsychotic and procognitive effects a compound must act as context- or region-specific dopamine D₂ receptor antagonist or agonist.

A dopamine D₂ receptor partial agonist has been postulated to provide relief from both cognitive and psychotic symptoms by essentially restabilizing aberrant dopamine signaling. Aripiprazole was developed and marketed as such a stabilizer;¹⁷⁹ however, despite its significant antipsychotic efficacy, procognitive efficacy has been limited.^{180,181}

Recent preclinical studies of biased signaling via the dopamine D₂ receptor may explain aripiprazole's lack of clinical procognitive efficacy. While this drug is a partial agonist at the dopamine D₂ receptor for G*ai*/o coupling and therefore cAMP signaling, it is comparable to dopamine D₂ antagonists in its inability to recruit β -arrestin-2.¹⁸² While β -arrestin-2 antagonism in the striatum contributes to antipsychotic efficacy,^{182–185} the potentiation of β -arrestin-2 recruitment in the PFC may be crucial for HPC–PFC-related cognitive outcomes. Recently, two aripiprazole analogues, UNC9994 and UNC9975, were shown to be β -arrestin-2 agonists in the PFC, but antagonists in the striatum.¹⁸⁶ Furthermore, UNC99-series compounds, but not aripiprazole, are able to activate GABAergic fast-spiking interneurons in the PFC, which are essential for synchronized cortical activity and are known to have impaired function in schizophrenia patients.^{187–189} Further preclinical assessment shows that UNC99-series compounds display simultaneous efficacy in both mouse models of positive symptoms and CIAS,¹⁹⁰ thus providing a template for agents with highly engineered biased signaling to treat a broader range of symptoms in the disorder.

3.3.3. Muscarinic Acetylcholine M₁ Receptor Agonists/PAMs. The M₁ receptor is highly expressed within HPC–PFC circuitry including the cortex, HPC, and striatum.¹⁹¹ Levels are lower in the CNS of schizophrenia patients,¹⁹² notably in the dlPFC¹⁹³ wherein lower M₁ binding potential in patients with schizophrenia significantly correlates with impaired performance in the Cambridge Neuropsychological Test Automated Battery (CANTAB).¹⁹⁴ Unfortunately, muscarinic receptors have a highly conserved orthosteric site, which has made the development of subtype-selective orthosteric agonists for the M₁ receptor very challenging.

Xanomeline, the muscarinic acetylcholine M₁/M₄ receptor-preferring agonist, has procognitive and antipsychotic efficacy

in rodent and nonhuman primate animal models of CIAS and schizophrenia.^{195–197} It was originally developed for the treatment of Alzheimer's disease, where it showed efficacy in treating behavioral disturbances and cognitive deficits (akin to those found in schizophrenia) in phase II clinical trials,¹⁹⁸ and versus positive and cognitive symptoms in a subsequent pilot study with schizophrenia patients.¹⁹⁹ Unfortunately, its use is heavily limited by side-effects largely mediated by other muscarinic receptor subtypes, notably severe gastrointestinal disturbances.^{198,200} Karuna Therapeutics aims to reduce these liabilities by coadministering xanomeline with the peripherally restricted antimuscarinic agent, tropium, and a phase II clinical trial assessing its safety and antipsychotic efficacy was completed in September 2019. The combination therapy was well-tolerated, and a phase III trial is planned by the end of 2020,²⁰¹ though it is not clear whether an assessment of procognitive efficacy will be included as an end point.

Amidst these studies, a phase Ib clinical trial sponsored by GlaxoSmithKline showed that the muscarinic M₁ receptor selective agonist, GSK1034702, was procognitive in a nicotine abstinence model with minimal to mild gastrointestinal side-effects.²⁰² This provided the first evidence that muscarinic M₁-selective ligands could produce procognitive effects in humans with minimal cholinergic side-effects. Whether these improvements in cognition could be replicated in patients with CIAS was never reported. GSK1034702 was removed from the GlaxoSmithKline pipeline in 2010; more recent studies have suggested that its subtype-selectivity and hence therapeutic index might be more limited than first estimated.²⁰³ Reportedly, more selective muscarinic M₁ receptor agonists have been developed and moved into clinical development, albeit for dementia, rather than CIAS. HTL-9936 progressed into phase I [NCT02291783], and HTL-18318 moved as far as a phase II trial. However, further development was voluntarily suspended due to unexpected toxicology findings in nonhuman primates.²⁰⁴

Various muscarinic M₁ receptor PAMs (e.g., VU0467319) are being developed to improve the subtype selectivity for the M₁ receptor, therefore avoiding the gastrointestinal side-effects associated with agonist activity at other subtypes. These ligands have a range of functional selectivity profiles and intrinsic agonistic activity^{205–209} with many displaying *in vivo* efficacy in animal models relevant to CIAS in the absence of gastrointestinal side-effects.^{210–212} However, clinical development of muscarinic M₁ receptor PAMs has been mostly early stage and limited to neurodegenerative diseases. The most advanced agent, MK-7622, progressed into phase II trials for Alzheimer's disease but did not significantly improve cognition in patients.²¹³ A notable side-effect was diarrhea, suggesting that M₁ receptor activation may contribute to GI effects in humans and that the degree of allosteric cooperativity and/or agonist activity for a PAM is an important factor in its safety profile.

3.3.4. Serotonin 5-HT₆ Receptor Antagonists. 5-HT₆ receptors are expressed exclusively postsynaptically within HPC–PFC circuitry,^{214,215} suggesting its primary function is regulating neurotransmission. 5-HT₆ receptor antagonists increase glutamatergic and cholinergic signaling in the HPC and PFC,^{216–218} and this mechanism is posited to underlie the consistent *in vivo* procognitive efficacy of 5-HT₆ receptor antagonists in behavioral tests and models relevant to CIAS,²¹⁹ though this approach has largely failed in clinical trials for neurodegenerative diseases.

Avineuro Pharmaceuticals has two 5-HT₆ antagonists in clinical development for the treatment of CIAS; AVN-211 (phase II/III) and AVN-322 (phase I/II). In a pilot study, AVN-211 significantly improved various measures of attention when compared to placebo.²²⁰ AVN-322 has greater selectivity for the 5-HT₆ receptor compared to AVN-211 and displays procognitive efficacy in preclinical models of CIAS across various behavioral tasks.²²¹ Phase I studies with AVN-322 suggest an excellent pharmacokinetic and safety profile following short-term exposure; the company suggests that this compound is ready to enter phase II trials.

3.3.5. Targeting Orphan GPCRs. There are nearly 400 nonodorant GPCRs in the human genome, of which around 110 are the target of approved drugs and a further 70 are targets of compounds in clinical trials.¹³⁶ Orphan GPCRs, receptors that have no known endogenous ligand, represent the majority of the remaining 220 unexploited GPCRs. This class of receptors may offer new insights into complex disease pathology or play distinct functional roles that can be exploited in the treatment of diseases with fewer side-effects. As such, developing compounds that target orphan GPCRs highly enriched within HPC–PFC circuitry offers a source of innovation that may help advance drug discovery for CIAS with greater translational relevance. Here we highlight recent breakthroughs in targeting two such receptors, GPR52 and GPR139.

The Gas-coupled orphan GPCR GPR52 is expressed exclusively in the brain and highly enriched within HPC–PFC circuitry, mostly coexpressed with dopamine D₂ receptors in the NAc and dopamine D₁ receptors in the PFC.^{222,223} As such, agonists of GPR52 could theoretically produce simultaneous antipsychotic and procognitive effects by counteracting Gai-coupled-D₂ receptor hyperactivity in the striatum while rescuing Gas-coupled-D₁ receptor hypoactivity in the PFC, respectively. GPR52 agonists developed by Takeda Pharmaceutical Company, 3-BTBZ (7m)²²⁴ and FTBMT (4u),²²⁵ display both antipsychotic and procognitive efficacy in preclinical models of schizophrenia.^{222,226} The mechanistic basis of cortical GPR52 signaling is slowly being elucidated; recent studies show that GPR52-mediated ERK1/2 signaling in frontal cortical neurons is β -arrestin-2-dependent²²⁷ and that cortical GPR52 regulates striatal function,²²³ providing insights into mechanisms of efficacy in HPC–PFC-related cognitive outcomes.^{228,229} Whether or not a β -arrestin-biased GPR52 agonist would produce better efficacy remains unknown. Further GPR52 agonists developed by Boeringer Ingelheim Pharma/Beacon Discovery and Sosei Heptares display procognitive effects related to cognitive flexibility in rodent models of CIAS,^{230,231} though their pharmacology is unknown. While still in the early stage of research, GPR52 is an exciting and novel target for the treatment of both psychosis and CIAS.

The G α_q -coupled orphan GPCR GPR139 is coexpressed with dopamine D₂ receptors in HPC–PFC circuitry.²³² It is also found in regions implicated in motivation and emotion and has emerged as a target for the treatment of cognitive and motivation deficits associated with schizophrenia. GPR139 knockout mice show impaired episodic-like memory, working memory, and motivation, while a GPR139 agonist reverses impaired cognitive flexibility in mouse models of CIAS.²³³ A phase II proof-of-concept clinical trial was completed in September 2019 assessing the procognitive and motivational efficacy of the GPR139 agonist TAK-041 as an add-on

treatment for schizophrenia patients with CIAS. While results are yet to be posted, TAK-041 remains an active program.

3.3.6. Other GPCR Targets. Other GPCRs not included above represent targets of interest for schizophrenia treatment due to their nondopaminergic mechanisms of action and antipsychotic efficacy at the preclinical and/or clinical level. These include metabotropic glutamate receptors (mGlu1, mGlu2/3, and mGlu5)^{234,235} and the muscarinic M4 acetylcholine receptor.^{236,237} While some of these targets and their ligands have a theoretical or even preclinical basis for procognitive efficacy,^{238,239} they are not reviewed herein as they have not been assessed clinically with CIAS as a primary end point.

4. PRECLINICAL BEHAVIORAL TASKS FOR CIAS

Even with appropriate therapeutic targets and mechanisms of action, the lack of a true “positive control” against CIAS limits the assessment of *in vivo* efficacy with any predictive validity. Many commonly employed cognitive behavioral tests for rodents do not reflect those used in the clinic, contributing to the overwhelming false-positive rate for compounds against CIAS.^{240,241} There is an urgent need for procognitive agents to be tested in preclinical cognitive *behavioral tasks* that probe the same processes in humans relevant for CIAS and rely on common neural mechanisms. Importantly, equal focus should be paid to selecting adequate *animal models* of CIAS. However, outlining the validity and limitations of animal manipulations is beyond the scope of this current review but has been documented extensively elsewhere.^{241–244}

Herein we highlight preclinical *behavioral tasks* recommended by the Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS) initiative, which identified tests from cognitive and clinical neuroscience that examine specific cognitive processes linked to CIAS-relevant neurocircuitry.^{245,246} Furthermore, we highlight operant touchscreen-based behavioral tasks based on the Cambridge Neuropsychological Test Automated Battery (CANTAB) that assess cognitive function in humans, nonhuman primates, and rodents. These rodent variants are similar, if not identical, to the original CANTAB tasks.^{247–250} As numerous studies have proven the utility of CANTAB testing in patients with CIAS,^{251–255} the ability to use a comparable touchscreen approach to measure cognition in rodents, nonhuman primates, and human patients may significantly improve the likelihood of successful translation of preclinical studies. Coupled with a greater potential for translation, these touchscreen-based cognitive tasks have many added benefits of operant automation including reduced experimenter interference and labor, and therefore improved standardization and reduced variability.²⁴⁸

4.1. Working Memory. Historically, working-memory performance in rodents has overwhelmingly been assessed using the T- or Y-maze tests.²⁵⁶ These maze tasks rely on a rodent's intrinsic tendency to alternate their choice and can be tested with and without the use of food rewards (Figure 4A), making them relatively quick tests that are not reliant on extended training sessions or food restriction. It is assumed that alternating behavior relies on spatial working memory due to a need to remember their initial choice in order to enter an alternative arm, and various lesion studies implicate functioning of key HPC–PFC nodes, although not exclusively.²⁵⁷ However, tasks based on the innate preference of rodents for novelty are arguably more dependent on short-term habitu-

ation than working memory processes.^{258,259} While schizophrenia patients can present with impairments in short-term habituation, working memory and short-term habituation rely on distinct neural mechanisms and differentially impact patient outcomes.²⁶⁰

The eight-arm radial arm maze (RAM) variant may be less reliant on a passive preference for novelty as there are considerably more arm entry options than the simpler win-shifting tasks, and it generally employs appetitive reinforced training²⁶¹ (Figure 4B). However, mice in this task readily adopt a clockwise or anticlockwise entry strategy, avoiding the need for active engagement of working memory processes and instead relying on spatial strategy development.^{262–264} This makes it difficult to determine whether compounds that improve performance in these tasks are improving working memory or are simply improving spatial strategy. Interestingly, humans partaking in a head-mounted display version of the RAM also readily adopt clockwise or anticlockwise entry strategies²⁶⁵ which only reinforces the poor face and construct validity of the RAM as a test of working memory as opposed to spatial strategy.

While CNTRICS have included the RAM in their recommendations for the preclinical assessment, they place a greater emphasis on operant delayed match to position (DMTP) and operant delayed nonmatch to position (DNMTP) tasks.²⁶⁶ Two-choice operant DMTP/DNMTP tasks involve the presentation of one retractable lever in a given position (left or right) during the sample phase, which is pressed to trigger a delay period. Following the delay period, both levers are presented, and the animal must press the lever that either matches (DMTP) or nonmatches (DNMTP) the sample phase position to obtain a reward (Figure 4C). Variations have also been made with two nose-poke holes in place of the two levers.^{267,268} However, these two-position paradigms face a common confound whereby animals can “solve” the task by preemptively positioning themselves in front of the correct position during the delay period by long-term habitual memory rather than relying on working memory processes.²⁶⁹

The trial unique nonmatch to location (TUNL) touchscreen task is a DNMTP test that has been developed to mitigate non-working-memory-dependent strategies by using multiple location pairs across trials, offering more trial types and less repetition of same trials, and therefore greater overall “trial uniqueness”.²⁷⁰ Along with improved face validity, improved construct validity over other working memory tasks is reflected in the similarities between the TUNL touchscreen task the CANTAB touchscreen spatial working memory task for use in humans and nonhuman primates.^{248,271} During TUNL, one of the possible locations on screen (5 for mice and 14 for rats) will illuminate and must be touched to trigger a delay period. After the delay period, the animal must return to the opposite side of the chamber in order to trigger the choice phase, thereby further mitigating mediating strategies. The animal is then presented with two illuminated locations and must touch the nonmatching location to receive a reward (Figure 4D). TUNL involves extensive training protocols,²⁷² but as multiple animals can be run in the task simultaneously, the overall time taken is similar if not less than nonautomated task variants.²⁴⁸ Performance in TUNL is dependent on intact HPC and PFC function in both mice and rats,^{270,272–275} however further validating studies assessing circuit function and synchrony during this task, e.g., by *in vivo* electrophysiology,^{276,277} would

provide further evidence for cross-species translatability of results in TUNL. Performance in TUNL appears to be impaired in multiple models of CIAS^{278–282} and it is notable that mGlu₂/mGlu₃ receptor activation (a mechanism that has largely failed in clinical trials) is unable to reverse CIAS model-induced deficits in TUNL.²⁸⁰ Overall, these data highlight the TUNL touchscreen task as a preclinical test of working memory with high face and construct validity and potentially high predictive validity for CIAS drug development and as a test which avoids confounds associated with traditional working memory tasks.

4.2. Cognitive Flexibility. Following the recommendation by CNTRICS that the CANTAB intradimensional/extradimensional (ID/ED) test of attentional-set shifting be used in clinical assessment of cognitive flexibility in patients with CIAS,²⁸³ CNTRICS further recommended the rodent version, odor ID/ED, be used in preclinical assessments.²⁸⁴ Odor ID/ED requires rodents to dig in bowls containing food reward by discriminating their choices based on two dimensions: type of digging medium and odor applied to the bowl. The task consists of three phases; compound discrimination (CD), ID shift, and ED shift, with each phase followed by a test of RL (Figure 4E). During CD, animals form an attentional set by learning to respond to a rewarded positive cue from the relevant dimension, i.e., odor 1 versus odor 2, while ignoring the irrelevant dimension, i.e., medium. During reversal, the previously negative cue becomes positive. ID shift is identical to CD except the specific odor and medium cues change. During the ED shift, the rewarded cue is from the previously irrelevant dimension, i.e., medium 1 versus medium 2, and the previously relevant dimension becomes irrelevant, i.e., odor. The number of trials taken to behaviorally shift responses to support the rule change is used as a measure of cognitive flexibility. The odor ID/ED task is notably similar to the human CANTAB task, varying only in the type of dimensions (odor/medium vs number/color/shape) and the behavioral response (digging in a bowl vs touchscreen). Indeed, the neural correlates required for odor ID/ED highly reflect those necessary for ID/ED performance in humans and nonhuman primates such as the intact function of key HPC–PFC nodes.^{285–288} Furthermore, deficits in odor ID/ED are observed in animal models of CIAS,^{289–291} while patients with CIAS display robust deficits in the CANTAB ID/ED task,^{292,293} making it a valuable assessor of cognitive flexibility with high face validity. However, odor ID/ED has to be administered entirely manually and is therefore very low-throughput.^{294,295} Additionally, odor-based cues can be difficult to systematically control, therefore contributing to variability. These limitations essentially preclude its use for CIAS drug development, rendering it incompatible with the need for early “go/no-go” decisions in CNS drug discovery.²⁹⁶

Although not recommended for clinical research, CNTRICS suggested the use of high-throughput RL paradigms for preclinical behavioral assessment primarily due to their relative ease of use. While RL can be assessed in rodents in a plethora of paradigms, the touchscreen visual discrimination and RL (VD/RL) task remains the most widely employed rodent touchscreen task. A unique benefit of the rodent touchscreen VD/RL paradigm is that it can be administered as part of a cognitive battery along with other tasks, e.g., TUNL and paired associate learning (PAL, *vide infra*), using the same apparatus,^{248,250} as for CANTAB in the clinic. In VD, animals first learn that responses to one of two stimuli (irrespective of

Figure 4. Schemes of various behavioral tasks used to assess the key cognitive processes dysfunctional in CIAS. In all cases, S^+ represents the correct choice, while S^- represents the incorrect choice. (A) T-maze rewarded alternation task. (B) Delayed nonmatch to position win-shift paradigm using the radial arm maze. (C) Two-lever operant tasks using either a delayed matching to position (DMTP) or a delayed nonmatching to position (DNMTTP) test. (D) Mouse trial unique nonmatch to location (TUNL) touchscreen task. (E) The rodent odor intradimensional/extradimensional (ID/ED) test of attentional set-shifting. (F) Touchscreen visual discrimination and reversal (VD/RL) task. (G) Simple novel object recognition task. (H) Touchscreen paired-associate learning (PAL) task, in this case the correct object–location pairs are flower–left, aeroplane–middle, and spider–right.

stimulus location) results in a reward. Following discrimination learning, the stimulus–reward contingency is reversed such that the previously unrewarded stimulus is now rewarded and vice versa (Figure 4F). Measuring the accuracy across RL sessions or the number of trials required to reverse the stimulus–reward association is used as a measure of cognitive flexibility. RL has been shown to rely on key neural mechanisms involved in cognitive flexibility processes such as HPC–NAc–Thal–PFC circuit node function, connectivity, and synchrony.^{276,297,298} Furthermore, deficits in RL have been

observed in some but not all models of CIAS.^{282,299–302} Adapting the touchscreen VD/RL paradigm to be more comparable to the CANTAB ID/ED attentional-set-shifting task would be beneficial to improve construct validity. However, attempts thus far have revealed significant obstacles to developing such a task especially for mice, including strain differences and challenges with the attributes of discrimination stimuli.³⁰³

4.3. Episodic Memory. The novel object recognition (NOR) task is one of the most popular preclinical cognitive

tasks that has been used to measure episodic-like memory.²⁹⁰ Like the Y-, T-, and radial arm mazes, NOR tasks rely primarily on a rodent's innate preference for novelty. Standard NOR assesses a rodent's ability to encode two identical objects (sample phase), then after a delay (or pharmacological insult), to recall this information when presented with both the familiar object and a novel object (choice phase) (Figure 4G). Intact memory is inferred by the animal spending more time interacting with the novel object. NOR is a favorable task due to its ease of use, simplicity, and lack of reliance on extensive training sessions or food restriction. Furthermore, interventions can be made during encoding, consolidation, and retrieval stages of the task.^{304,305} However, NOR does not readily reflect any episodic memory tasks used in the clinic, thus it is not recommended by CNTRICS for use in preclinical assessments of CIAS.³⁰⁶ Furthermore, the single-trial nature of NOR is more reliant on familiarity-based episodic memory, which in rodents is independent of the HPC,^{307,308} an issue for translation as patients with CIAS do not show impairments in familiarity-based episodic memory but rather recollection-based episodic memory, which is HPC-dependent and relies on intact HPC–EC–PFC circuitry.³⁰⁹ CNTRICS opted instead to recommend the rodent touchscreen object-location paired-associate learning (PAL) task.^{310–312} Patients with CIAS display significant deficits in the CANTAB-PAL task, and their performance significantly correlates with symptom severity and functional capacity.^{313–315} In the rodent touchscreen PAL, animals learn to associate three different stimuli with each of the three touchscreen locations to form an object–location association (dPAL). In a simpler version of the task, (sPAL), two identical stimuli (objects) are presented in two locations: one in the correct location and the other in an incorrect location so that animals learn a conditional rule such as “if A, then select the left; if B, then select the right” (Figure 4H). Importantly, performance in dPAL relies on intact HPC and PFC function^{302,312,316} suggesting it likely requires engagement of recollection-based episodic memory processes. However, investigating the role of the EC in this task will be required to maximize face validity. Rodent PAL acquisition is impaired in mouse models of genetic risk for schizophrenia,²⁵⁰ while PAL recall is impaired in some but not all preclinical models of CIAS.^{302,312} Although greater validation is likely required, rodent PAL appears to have strong potential as a translational tool with greater relevance for CIAS than previously used tasks of episodic-like memory.

5. CONCLUDING REMARKS

Drug development for CIAS has been both challenging and largely underwhelming. Despite major efforts and initiatives to increase the amount of research into CIAS, there remains no adequate treatment option. This striking translational bottleneck highlights the need for a cohesive, translational drug development strategy to improve the likelihood that procognitive effects observed at the preclinical level can be reflected in the clinic. In this review, we describe HPC–PFC circuits that regulate brain function and behavior relevant to CIAS across mammalian species and the ways our understanding of these circuits can be applied to multiple facets of preclinical drug discovery to improve translation. HPC–PFC circuit function can be used as a source of innovation for identifying novel therapeutic targets such as circuit-enriched orphan GPCRs, or more established targets that could be tackled with contemporary pharmacological approaches, such

as allosteric modulation or biased agonism, to alter HPC–PFC circuit function with greater nuance. We also suggest that the procognitive efficacy of investigational compounds be assessed using cognitive paradigms with the greatest face validity (in that they rely on intact HPC–PFC circuit function) and high construct validity (in that they reflect the assessment tasks commonly used in the clinic). To this end, we propose the touchscreen cognitive tasks adapted from those used in humans and nonhuman primates have the greatest translational potential, particularly when used as a cognitive battery as that are undertaken in the clinic.

Combining mechanisms of action at HPC–PFC circuit-enriched targets with preclinical behavioral tests relying on intact HPC–PFC circuit function offers a uniquely cohesive, translation-focused approach to preclinical drug development for CIAS. Validating and applying this approach may ultimately improve the translational bottleneck and finally result in adequate therapeutic options for patients suffering with CIAS.

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Notes

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ABBREVIATIONS

CANTAB, Cambridge Neuropsychological Test Automated Battery; CD, compound discrimination; CIAS, cognitive impairments associated with schizophrenia; CNTRICS, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia; dlPFC, dorsolateral prefrontal cortex; DMTP, delayed match to position; DNMT, delayed nonmatch to position; dPAL, different paired-associate learning; EC, entorhinal cortex; ED, extradimensional; ERK, extracellular signal-regulated kinase; GPCR, G protein-coupled receptor; HPC, hippocampus; HPC–PFC, hippocampal–

prefrontal cortical; ID, intradimensional; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NOR, novel object recognition; NRe, nucleus reuniens; PAL, paired-associate learning; PAM, positive allosteric modulator; PC, perirhinal cortex; PFC, prefrontal cortex; PHC, parahippocampal cortex; RAM, radial arm maze; RL, reversal learning; sPAL, same paired-associate learning; TUNL, trial unique nonmatch to location; VD, visual discrimination; VTA, ventral tegmental area

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■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on October 28, 2020 with a caption incorrectly ordered for Figure 4E–H. The corrected version was posted on November 17, 2020.