Schizophrenia Research 207 (2019) 80–92

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Improving cognitive training for schizophrenia using neuroplasticity enhancers: Lessons from decades of basic and clinical research

G.D. Guercio [a,b,*], M.E. Thomas [b], J.M. Cisneros-Franco [b], P. Voss [b], R. Panizzutti [a], E. de Villers-Sidani [b,**]

[a] Biomedical Sciences Institute, Federal University of Rio de Janeiro, RJ, Brazil
[b] Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, QC, Canada

ARTICLE INFO

Article history:
Received 19 October 2017
Received in revised form 13 April 2018
Accepted 17 April 2018
Available online 3 May 2018

Keywords:
Neuroplasticity
Cognition
Biomarkers
Personalized medicine
Cognitive remediation therapy
Precision psychiatry

ABSTRACT

Mounting evidence indicates that schizophrenia is a disorder that stems from maladaptive plasticity within neural circuits and produces broad cognitive deficits leading to loss of autonomy. A large number of studies have identified abnormalities spanning many neurotransmitter systems in schizophrenia, and as a result, a variety of drugs have been developed to attempt to treat these abnormalities and enhance cognition. Unfortunately, positive results have been limited so far. This may be in part because the scope of abnormalities in the schizophrenic brain requires a treatment capable of engaging many different neurotransmitter systems. One approach to achieving this kind of treatment has been to use neuroplasticity-based computerized cognitive training programs to stimulate the formation of more adaptive circuits. Although the number of studies implementing this approach has increased exponentially in recent years, effect sizes for cognitive gains have been modest and adherence to treatment remains an important challenge in many studies, as patients are often required to train for 40 h or more. In the present paper, we argue that cognitive training protocols will benefit from the addition of cognitive enhancers to produce more robust and longer lasting targeted neuroplasticity. Indeed, recent data from animal studies have provided support for combining plasticity-enhancing drugs with tailored behavioral training paradigms to restore normal function within dysfunctioning neural circuits. The advantages and challenges of applying this approach to patients with schizophrenia will be discussed.

1. Introduction

Cognitive deficits are a core feature of schizophrenia for which there is no adequate treatment. It is imperative to treat these deficits because they are the best predictors of a patient's long-term functional outcome (Harvey et al., 1998; Kitchen et al., 2012; Nuechterlein et al., 2011). Many neurotransmitter and neuromodulatory systems important for cognition and neuroplasticity are altered in schizophrenia, such as the dopaminergic, glutamatergic, cholinergic, and oxytocinergic systems. For this reason, several drugs targeting these systems have been used in clinical trials but with limited efficacy so far.

Another strategy for treating cognitive deficits is the use of computerized neuroplasticity-based training that targets specific cognitive functions impaired in schizophrenia. Although current evidence indicates that such training programs can be effective at improving cognition, effect sizes are generally small to medium, and they often require many hours to be effective, raising the issue of subject compliance in real-world settings (McGurk et al., 2007; Wykes et al., 2011).

Because drugs that enhance neuroplasticity may increase the effectiveness of cognitive training regimens that are dependent on plastic neural circuits, Swerdlow (2012) proposed that combining both strategies could achieve synergistic results in schizophrenia. Here we will build on this idea by presenting evidence of impaired neuroplasticity in schizophrenia and by examining the findings of many studies using pharmacological and cognitive training interventions. We will discuss recent studies that have attempted this approach and propose novel strategies to optimally harness the neuroplasticity-enhancing effects

Abbreviations: ACh, acetylcholine; AMPA, a-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid; COMT, Catechol-O-Methyltransferase; CSF, cerebrospinal fluid; DAAO, D-amino acid oxidase; D_1R, dopamine type 1 receptors; D_2R, dopamine type 2 receptor; dlPFC, dorsolateral prefrontal cortex; LTP, long-term potentiation; mAChR, muscarinic receptor; MMN, mismatch negativity; nAChR, nicotinic receptor; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; PCP, phencyclidine; PET, positron emission tomography; PPI, prepulse inhibition of startle; TMS, transcranial magnetic stimulation.

* Correspondence to: G.D. Guercio, Av. Carlos Chagas Filho, 373, CCS/ICB/Bl. F1-lab.03. Ilha do Fundão, Rio de Janeiro, RJ, Brazil.
** Correspondence to: E. de Villers-Sidani, 3801 University Street, Room 742, Montreal, Quebec, Canada.
E-mail addresses: gerson.biomed@gmail.com (G.D. Guercio), etienne.de-villers-sidani@mcgill.ca (E. de Villers-Sidani).

https://doi.org/10.1016/j.schres.2018.04.028
0920-9964/

of specific drugs to be used in combination with targeted cognitive training approaches.

2. Abnormal plasticity in schizophrenia

Although neuroplasticity is an essential feature of our central nervous system that allows it to adapt both function and structure in response to an ever-changing environment, its mechanisms can be maladaptive in certain disease states and may contribute to the acquisition and maintenance of symptoms. Maladaptive plasticity refers to plasticity that disrupts normal function. Tinnitus, the phantom perception of noise or ringing in the ears, constitutes a relevant example of maladaptive plasticity that generally appears in some individuals following hearing loss-induced deafferentation (Axelsson and Ringdahl, 1989). The development of tinnitus is associated with plastic changes in the auditory cortex that lead to a distortion of the cortical representation of sound frequencies, which in turn contributes to the phantom percept (Engineer et al., 2013).

Similarly, schizophrenia may constitute another example of altered sensory systems giving rise to abnormal plasticity. For instance, mismatch negativity (MMN)—a standard electrophysiological marker of early auditory processing that relies on short-term plasticity—deficits are a consistent finding in schizophrenia research (Erickson et al., 2016). Additionally, some studies show that auditory cortex dysfunction becomes worse as the disease progresses (Salisbury et al., 2007). Therefore, it is possible that the functionally impaired sensory cortex in schizophrenia produces downstream mechanisms that disrupt the functional and structural integrity of higher-order brain regions, such as the prefrontal cortex, thus contributing to the emergence of various cognitive deficits (Vinogradov and Nagarajan, 2017).

Functional magnetic resonance imaging can uncover localized alterations in plasticity that may help explain cognitive deficits observed in schizophrenia. For instance, when performing a working memory task, patients with schizophrenia present hypoactivation in the prefrontal cortex (Subramaniam et al., 2014), as well as aberrant (and perhaps deleterious) functional connectivity between the prefrontal cortex and the hippocampus (Meyer-Lindenberg et al., 2005). In addition, the ability to discriminate between internal thoughts from external stimuli may be impaired in schizophrenia, in part because they have a hypoactive reality monitoring network (Subramaniam et al., 2014). Compelling additional evidence of abnormal plasticity comes from studies using transcranial magnetic stimulation that revealed deficits in long-term potentiation (LTP) and long-term depression (LTD) in schizophrenia (Cavuş et al., 2012; Daskalakis et al., 2008; Mears and Spencer, 2012; Strube et al., 2015). A large-scale proteomic and genomic analysis provided strong evidence of alterations in the expression of many proteins directly involved LTP and calcium signaling, as well as in the postsynaptic density (Föcking et al., 2015). In addition, pyramidal cell somal volume, and dendritic spine density and number are reduced in the auditory cortex of patients with schizophrenia (Parker and Sweet, 2017). The aforementioned abnormalities, therefore, may be the consequence of dysfunctional neuronal machinery that itself results from impaired synaptic plasticity.

3. Systems targeted by neuroplasticity-enhancing drugs

Abnormal plasticity in schizophrenia is hypothesized to be in part the result of neurochemical alterations in several neurotransmitter and neuromodulatory systems (Forsyth and Lewis, 2017). In particular, the GABAergic and glutamatergic neurotransmitter systems and many neuromodulators (dopamine, acetylcholine, oxytocin, serotonin, norepinephrine, and others) are critical neuroplasticity regulators and thus are key targets for the development of drugs designed to improve cognition in schizophrenia. Here we review evidence of dysregulation in four major neurotransmitter and neuromodulatory systems in schizophrenia and of efforts to improve cognition using drugs targeting them. We chose to not include drugs targeting the GABAergic, serotonergic or norepinephrinergic systems, because we believe the currently available drugs targeting them may not act synergistically when combined with the cognitive training regimens discussed here (for reviews on these drugs, see (Maletic et al., 2017; Rudolph and Möhler, 2016; Švob Štrac et al., 2016)).

3.1. The dopaminergic system

Dopaminergic neurons in the dorsal substantia nigra signal salient events (Comoli et al., 2003). Their projections to the dlPFC predominantly target D_1Rs found in the dendritic spines of layer 3 pyramidal cells and the sustained firing of these cells is required for working memory (Goldman-Rakic, 1995). Importantly, optimal levels of dopaminergic stimulation in the PFC modulate LTD and LTP (Otani et al., 2015) and improve working memory by reducing noise through the facilitation of lateral inhibition and reduction in glutamate release (Arnsten et al., 2015).

Evidence for the pro-cognitive effects of D_1R activation comes from both animal and human studies (Arnsten et al., 2017). In monkeys, administration of a D_1R agonist reverses haloperidol-induced working memory deficits, an effect that can last for more than a year after discontinuation of treatment (Castner et al., 2000). Moreover, Vijayraghavan et al. (2007) showed that D_1R stimulation in behaving monkeys enhances spatial tuning in PFC neurons. Similarly, a recent study found that D_1R activity is necessary to restore attention following a distracting stimulus (Jacob et al., 2016).

Interestingly, neurons within the PFC of schizophrenia patients show an extensive dendritic loss (Garey et al., 1998), reduced cell size, and impaired activity in layer 3 pyramidal cells (Arion et al., 2015). In addition, a positron emission tomography (PET) study revealed that schizophrenia patients have a reduced number of D_1Rs in the PFC, a reduction that correlates with negative symptoms and cognitive impairments (Okubo et al., 1997). Finally, patients have a blunted capacity to release dopamine in the dlPFC that may explain the reduced dlPFC activation observed during working-memory tasks (Slifstein et al., 2015). Such abnormalities may explain why patients with schizophrenia have working memory deficits (Frydecka et al., 2014; Park and Holzman, 1992).

To date, three D_1R agonists have been tested in patients with schizophrenia for the treatment of cognitive deficits. In a single dose, randomized, cross-over study of dihydrexidine and placebo, researchers found only a trend towards improved word association and verbal learning (George et al., 2007). Although there were no significant effects on cognition with dihydrexidine, a subsequent study with a small sample-size using the dihydrexidine enantiomer DAR-0100A showed improvements in working memory in schizotypal personality disorder (Rosell et al., 2015). In contrast, a more recent study with a larger sample failed to find any significant effect on working memory after three weeks of intermittent administration of DAR-0100A in patients with schizophrenia (Girgis et al., 2016). Finally, in another study with a limited sample size due to drug safety concerns, treatment with the D_1R agonist pergolide tended to improve working memory, verbal learning, and executive function (McClure et al., 2010). In sum, notwithstanding the ample evidence for the role of D_1R in cognition, efforts to increase its activity in patients with schizophrenia have yielded mixed results, perhaps because enhancing D_1R activity alone cannot change the maladaptive neural circuits formed throughout a patient's life.

3.2. The glutamatergic system

Excitatory neurotransmission in the brain is mainly achieved through glutamatergic activation of the ionotropic a-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors (Kew and Kemp, 2005). AMPA receptors are primarily involved in glutamate-dependent depolarization of

excitatory synapses. In contrast, the NMDA receptor (NMDAR) acts as a coincidence-detector that requires both the concomitant binding of an agonist (glutamate) and a co-agonist (D-serine or glycine), in addition to the depolarization of the postsynaptic membrane, to be activated. The NMDAR plays critical roles in neuroplasticity, memory, and cognitive function in general. In fact, activation of an NMDAR triggers many processes required for LTP, such as calcium influx, gene expression, and protein synthesis (Kandel, 2001).

Substantial evidence indicates that NMDAR hypofunction is a convergence point for schizophrenia symptoms (Balu, 2016; Guercio and Panizzutti, 2018). Hence, the role of D-serine as an NMDAR co-agonist and its requirement for LTP and LTD (Papouin et al., 2012) have prompted investigations of its relationship with schizophrenia. D-Serine is degraded by D-amino acid oxidase (DAAO), which is activated by G72, and polymorphisms of the G72 gene are associated with schizophrenia (Chumakov et al., 2002). Although one study found no difference between patients with schizophrenia and controls (Fuchs et al., 2008), most studies found lower blood D-serine levels in patients with schizophrenia (Bendikov et al., 2007; Calcia et al., 2012; Hashimoto et al., 2003), a finding that was corroborated by a recent meta-analysis (Cho et al., 2016). Remarkably, variants in the gene for serine racemase, the enzyme that forms D-serine from L-serine, have also been associated with schizophrenia (Balu et al., 2013; Labrie et al., 2012).

Since the link between NMDARs and schizophrenia has been established, many strategies have been tested to increase NMDAR activity, including increasing AMPA activity to indirectly activate NMDARs, the administration of glycine and D-serine, the use of glycine reuptake inhibitors, and the administration of D-cycloserine, a partial agonist at the glycine modulatory site. Although a pilot study found that CX516, a positive modulator of the AMPA receptor, improved cognition in schizophrenia (Goff et al., 2001), subsequent work with a greater number of patients failed to find an effect (Goff et al., 2008). Furthermore, sarcosine and bitopertin, both glycine reuptake inhibitors, were tested for cognitive enhancement in schizophrenia. Although evidence for sarcosine remains mixed (Amiaz et al., 2015; Lin et al., 2017; Tsai et al., 2004), bitopertin is ineffective for improving cognitive and negative symptoms in patients with schizophrenia (Bugarski-Kirola et al., 2017; Kantrowitz et al., 2017).

In contrast, the results with D-serine have been mixed, in part because of the different doses used, as one study investigating multiple doses observed that the higher doses (≥60 mg/kg), but not the lowest one (30 mg/kg), improved cognition in schizophrenia (Kantrowitz et al., 2010). Other studies in patients with chronic schizophrenia confirmed that doses above 30 mg/kg improved MMN as well as neurocognitive and clinical symptoms of schizophrenia, whereas bitopertin did not produce such improvements (Kantrowitz et al., 2018). Finally, a recent meta-analysis concluded that although D-serine is indeed effective for improving many schizophrenia symptoms, the effect sizes remain small to medium (Cho et al., 2016; Kantrowitz et al., 2018). In sum, evidence indicates the existence of a dysfunction of NMDARs in schizophrenia and that the administration of D-serine can improve cognitive deficits.

3.3. The cholinergic system

The cholinergic system is one of the most important modulatory systems in the brain, as it innervates a wide range of cortical and subcortical regions and is particularly known for its critical role in attentional processes and for modulating neuroplasticity. Acetylcholine (ACh), the main neurotransmitter of the cholinergic system, is released from presynaptic neurons and acts on postsynaptic nicotinic (nAChR) and muscarinic (mAChR) receptors. The basal forebrain complex, originating in the nucleus basalis and projecting to nicotinic and muscarinic receptors in many cortical regions, is considered a major hub of cholinergic modulation of cognitive processes (Lucas-Meunier et al., 2003). Activation of the nucleus basalis has been consistently shown to be a key regulator of experience-dependent plasticity in the adult brain (Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998; Puckett et al., 2007).

There is accumulating evidence of a cholinergic system dysfunction in schizophrenia. Decreased levels of nAChRs were found in many brain regions of schizophrenia patients, including the hippocampus and the prefrontal cortex (Breese et al., 2000). Importantly, antagonism of the mAChRs in non-psychotic individuals results in a syndrome with schizophrenia-like symptoms (Barak, 2009). *Post-mortem* analyses indicate that the production of acetylcholine might be impaired in the striatum in schizophrenia (Holt et al., 2005, 1999).

The high prevalence of smoking in patients with schizophrenia and the fact that some cognitive abnormalities can be improved by nicotine through smoking or other means has led some authors to hypothesize that smoking constitutes a form of self-medication (Kumari and Postma, 2005). Subsequently, using TMS to investigate LTD-like plasticity, Strube et al. (2015) showed that plasticity deficits in schizophrenia may be ameliorated by smoking.

Furthermore, transdermal nicotine patches in nonsmoking patients with schizophrenia improve attentional performance (Barr et al., 2008) and delayed recognition memory (Myers et al., 2004). Similarly, a nicotine nasal spray in a double-blind placebo-controlled study was found to decrease reaction time and improve performance in a spatial working memory task (Smith et al., 2006). Modulation of nicotinic receptors has been attempted with more selective ligands. For instance, TC-5619, an alpha-7 nicotinic receptor partial agonist, has produced mixed results (Lieberman et al., 2013; Walling et al., 2016). In addition, a large study using the partial agonist encenicline revealed improvements in cognition across multiple measures with medium effect sizes (Keefe et al., 2015), and research into promising new alpha-7 nicotinic agonists to enhance cognition is ongoing and warrants replication (Gee et al., 2017; Haig et al., 2016).

Another strategy to enhance cholinergic activity is to inhibit acetylcholinesterase, the enzyme that degrades acetylcholine. Importantly, acetylcholinesterase inhibitors improve learning and plasticity in aged rats (Voss et al., 2016). A study using donepezil (5 mg/day, for 12 weeks) concluded that it was not effective compared to placebo as an add-on treatment for the improvement of cognitive impairment in schizophrenia, but the large effect of placebo observed may have concealed any drug effect (Keefe et al., 2008). More recently, the same dose of donepezil showed potential in treating working memory and speed of processing in schizophrenia (Zhu et al., 2014). Although initial studies investigating galantamine, a drug that not only inhibits acetylcholinesterase but also acts as a positive allosteric modulator of different types of nAChRs (Samochocki et al., 2003), found positive effects on memory and attention, (Schubert et al., 2006), visual recognition (Lee et al., 2007), and processing speed and verbal memory (Buchanan et al., 2008), a subsequent study where patients received exclusively long-acting injectable risperidone found no ameliorative effects of galantamine on cognition (Lindenmayer and Khan, 2011).

All in all, the cholinergic system offers many pharmacological targets, but also great complexity in choosing one of many approaches. There is plenty of evidence for its involvement in schizophrenia and its disruption worsens symptoms and leads to a poorer functional outcome. However, evidence supporting the value of the cholinergic system as a key therapeutic avenue remains mixed.

3.4. The oxytocinergic system

Oxytocin is a peptide that can reach targets both through classical axonal release and through somatodendritic release and diffusion to the subarachnoid space (Shilling and Feifel, 2016). Oxytocin plays an important role in shaping behavior, notably affecting maternal behavior, social bonding, and social cognition in mammals (Ross and Young, 2009). In addition, oxytocin is also known to affect learning abilities and neuroplasticity in many brain regions (Sarnyai and Kovács, 2014).

Work done in humans has spurred the notion that oxytocin can have therapeutic value due to its role in social cognition. For instance, the intranasal administration of oxytocin increases the recognition of masked emotional faces (Schulze et al., 2011), and emotion recognition in general (Lischke et al., 2012). Oxytocin can also improve empathic accuracy in less socially-proficient individuals (Bartz et al., 2010). Importantly, patients with schizophrenia exhibit impairments in precisely these social cognitive domains (Green et al., 2015). Finally, social cognitive deficits are stable and present from the prodromal stage (Horan et al., 2012), suggesting a key role for oxytocin in schizophrenia.

Evidence supporting a relationship between oxytocin and schizophrenia comes from studies demonstrating that lower levels of oxytocin in the cerebrospinal fluid (CSF) were associated with more severe negative symptoms in patients (Sasayama et al., 2012). Single nucleotide polymorphisms at the oxytocin receptor were significantly associated with worse performance on social cognition and social perception tasks (Davis et al., 2014b). Moreover, a recent review of several clinical studies described an association between oxytocin and negative symptoms of schizophrenia (Shilling and Feifel, 2016).

Many clinical studies have attempted to improve cognition through the intranasal administration of oxytocin based on results from preclinical models. However, the results have been mixed. Daily intranasal oxytocin treatment over 14 days improved theory of mind (Pedersen et al., 2011) and a six-week treatment found improvements in fear recognition and empathy (Gibson et al., 2014). Moreover, an acute oxytocin treatment improves patients' ability to understand deceitful and sarcastic communication (Woolley et al., 2014). In contrast, other studies could not find any positive effect of oxytocin on psychosocial functioning (Cacciotti-Saija et al., 2015; Caravaggio et al., 2017). In sum, as is the case with all drug classes tested so far, it is unlikely that modifying one particular neurotransmitter system alone will improve the wide-ranging deficits observed in schizophrenia.

3.5. Summary

Although compelling evidence shows that the aforementioned systems are dysfunctional in schizophrenia, and therefore likely contribute to abnormal plasticity (Table 1), this has not resulted in new drugs being incorporated into clinical practice because of a lack of strong and reliable effects on cognition. Because we believe such drugs will be more useful when combined with a non-pharmacological therapeutic context, we will discuss how their administration can act synergistically with cognitive training.

4. Cognitive training

Despite our incomplete understanding of the pathophysiology of schizophrenia, its manifestations are most likely the result of impaired neural representations that likely result from maladaptive neuroplastic mechanisms. A traditional view of brain plasticity was that it could only take place during early developmental time windows known as critical periods and that afterward, the brain's circuits would be more or less fixed (Hensch, 2005). Such a view implies that mental disorders are harder to treat after a person reaches maturity. However, recent studies have shown that the brain can significantly change even after the closure of those critical periods (de Villers-Sidani et al., 2010; Recanzone et al., 1993; Voss et al., 2017).

For instance, transecting the median nerve of an adult monkey – which innervates the hand – produces a striking remodeling of the somatotopic map, and causes an expansion of the representation of the surrounding areas into the deafferented cortex (Merzenich et al., 1983). Moreover, Merzenich et al. (1984) amputated the fingers 2 and 3 and observed a decrease in the cortical receptive field size of these fingers coupled with an increase in the receptive field of the sparred fingers. This implies that removing the normal afferents inputs of a cortical area causes it to reorganize itself so that it becomes responsive to the surrounding non-deafferented area. Importantly, such neuroplasticity has been demonstrated in other sensory systems as well (Buonomano and Merzenich, 1998).

The pioneering work of Dr. Merzenich and others has suggested that we can harness this neuroplastic property of the adult brain to form more adaptive brain circuits in a targeted manner. One way to achieve this is by ensuring that the brain is actively engaged in a rewarding training that has enough repetitions and an appropriate difficulty level (Vinogradov et al., 2012). For example, passive auditory tone exposure in adult monkeys does not change the representation of frequencies in the auditory cortex, whereas operant frequency discrimination training—a paradigm where animals are rewarded for correct responses—induces plastic changes in the frequency representation of auditory cortical neurons, whose magnitude correlates with learning performance (Recanzone et al., 1993). Importantly, an active operant training is more effective at inducing cortical plasticity than classical conditioning (Blake et al., 2006).

Since many studies have found perceptual and higher-order cognitive deficits in patients with schizophrenia, it is tempting to speculate that brain training protocols could result in the formation of more adaptive circuits through experience-dependent plasticity (Vinogradov et al., 2012). To this end, researchers have used specifically designed cognitive

Table 1
Neurotransmitter/neuromodulatory systems commonly targeted for cognitive enhancement in schizophrenia. Despite strong evidence of alterations in these four systems, targeting them with a variety of drugs has resulted in disappointing results, and none of these drugs have been approved for treating cognitive deficits in schizophrenia.

System	Potential as a target of neuroplasticity-enhancing drugs	Involvement in Schizophrenia	Evidence of enhanced learning when targeting this system
Dopaminergic	D1R activation in the PFC regulate LTP/LTD, reduces noise and improves working memory	Reduced number of D1R and dendritic loss in the PFC, possibly underlying the working memory deficits	In monkeys, D1R agonist reverses haloperidol-induced working memory deficits, enhances spatial tuning in the PFC and improves attention; In schizophrenia evidence is mixed
Glutamatergic	NMDAR is critically involved in plasticity; drugs that increase its activity modulate LTP and LTD and improve many aspects of cognition and plasticity	Reductions in D-serine and NMDAR, genetic alterations in genes involved in the NMDAR signaling, which may underlie deficits in LTP and LTD in the disorder	Plenty of animal data shows the importance of the NMDAR for plasticity and cognition; In schizophrenia evidence favors D-serine
Cholinergic	Acetylcholine release is a trigger for neuroplasticity, being able to induce reorganization in the sensory cortex and improve learning; smoking improves neuroplasticity in schizophrenia (assessed by TMS)	Lower availability of mAChR in many brain regions, decreased levels of nAChRs in the forebrain, reduction of cholinergic interneurons in the striatum	Nicotine improves cognition and plasticity in schizophrenia; Other cholinergic agents, while effective in preclinical studies, have yielded mixed results in schizophrenia
Oxytocinergic	Influences gaze direction when looking at faces, stimulates prosocial behavior, modulates amygdala activity, improves social cognition	Lower levels of oxytocin in the CSF and genetic alterations of the oxytocin receptor; deficits in social cognition	Oxytocin may improve theory of mind and emotion recognition in schizophrenia; However, its administration alone does not influence psychosocial functioning

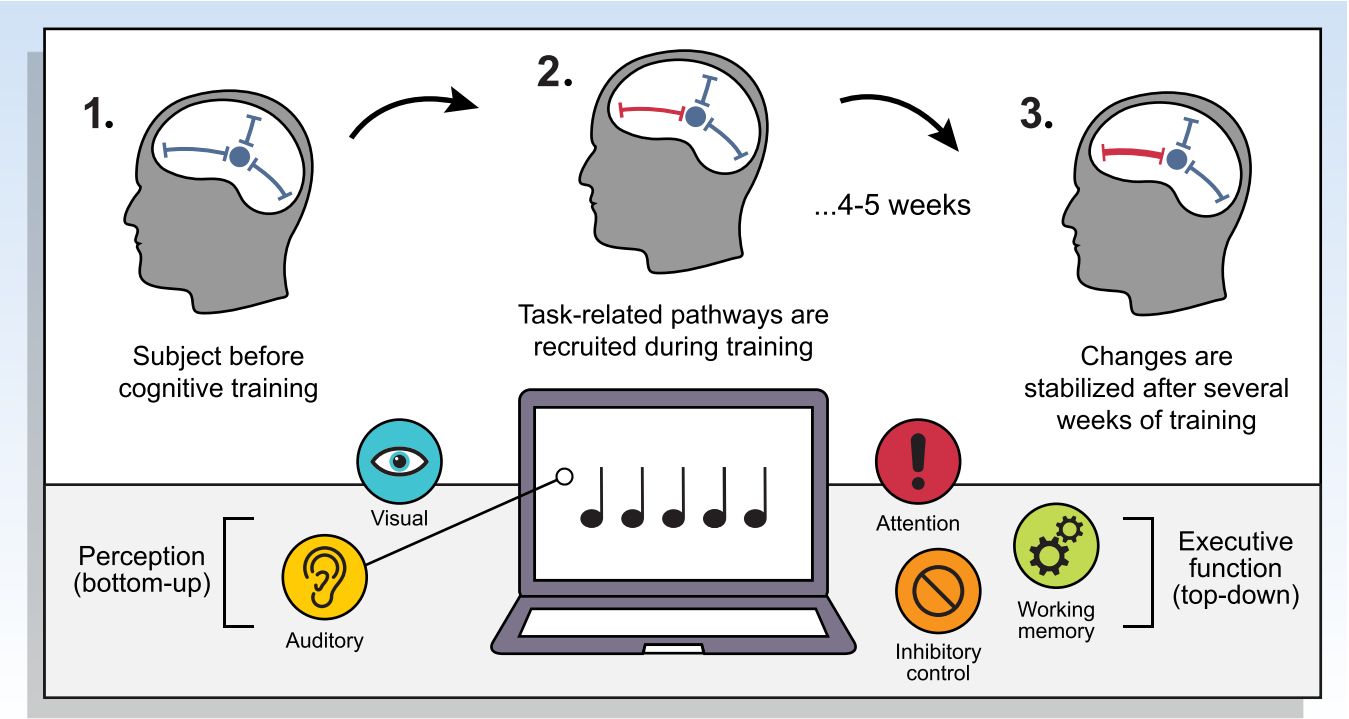

Fig. 1. Cognitive training as treatment for schizophrenia. Cognitive training exercises are used in both healthy and clinical populations to change neural circuits related to perception and cognition through non-pharmacological means. Usually performed on a computer, cognitive training can target both bottom-up and top-down aspects of cognition such as auditory tone discrimination, working memory, and attention in a controlled, precise, and personalized manner. In people with schizophrenia, cognitive gains achieved with training are typically correlated with functional effects and reductions in medical costs related to treatment. The success of training is, however, limited by patient compliance, as many hours of consistent training over weeklong periods are required for experience-dependent plastic changes to become stable.

exercises in a reproducible, extensive, and adaptive manner. Presentation of the exercises can take different forms, but computers have made it possible to present controlled and personalized exercises (Fig. 1). This contrasts with the unrestrained and unpredictable approaches used in many forms of psychotherapy.

In principle, any cognitive process can be the target of a cognitive training program. As such, a myriad of different training programs has been tested with various combinations of cognitive exercises of different durations. Typically, studies require patients to train 3–5 h per week for 4–8 weeks. Examples of types of training are working memory tasks (Lawlor-Savage and Goghari, 2014), auditory tone discrimination (Adcock et al., 2009) and even social cognition training (Nahum et al., 2014). Two meta-analyses found small to moderate positive effects of cognitive training in schizophrenia, but neither found specific variables (i.e., hours of training, type of training, participants' characteristics) that could explain the variety of outcomes (McGurk et al., 2007; Wykes et al., 2011). This may be the result of the common practice of training a broad array of cognitive functions simultaneously in patients, but could also result from a lack of specificity of the cognitive training exercises used in treating the cognitive deficits.

Several studies have shown that cognitive training can improve cognition in schizophrenia, and many neuroimaging studies have demonstrated complementary evidence of its neuroplasticity-inducing effects. For instance, 80 h of cognitive training was shown to restore both medial prefrontal cortex activity and behavioral performance in a reality monitoring task in patients with schizophrenia (Subramaniam et al., 2012). In addition, cognitive training improved working memory performance, which in turn correlated with increased activity in the middle frontal gyri (Subramaniam et al., 2014). These and many other studies have shown that schizophrenia does not deprive the brain of its capacity to undergo extensive neuroplasticity. However, not all deficits appear to be reversible following training. For instance, although auditory cognitive training enhances the MMN response in healthy subjects (Menning et al., 2000), Biagianti et al. (2017) showed that MMN deficits are not improved in schizophrenia following cognitive training. This is perhaps the result of impaired plasticity in schizophrenia.

Despite the fact that many recent studies have used more specific types of training in an attempt to target specific cognitive functions, the limited effect sizes of their results make it uncertain whether these interventions would prove successful in a clinical setting. As evidence indicates that cognitive gains correlate with functional effects (Fisher et al., 2010; Wykes et al., 2012), and with reductions in medical costs (Reeder et al., 2014), cognitive training protocols that result in greater cognitive enhancing effects may have higher therapeutic value. Moreover, any behavioral training requires a high level of commitment by the patient, and so a patient's satisfaction with training might be arguably central to the training's effectiveness (Rose et al., 2008). Remarkably, a patient's satisfaction with training and self-esteem correlates with the degree of cognitive improvement with training (Rose et al., 2008). Taken together, these studies suggest that training regimens that result in higher cognitive gains may have more clinical value.

4.1. Challenges for implementing cognitive training

Nonetheless, despite the seemingly side-effect free nature of these treatments, their clinical value will also depend on how quickly they result in real-life changes, as it is reasonable to assume that training programs that require a lot of effort from patients with mental disorders (especially schizophrenia) would have a high dropout rate. Furthermore, it is important to highlight that most cognitive training studies in schizophrenia were conducted among clinically stable participants. But patients with schizophrenia are often more symptomatic and less functional than this select group generally studied, meaning that studies less selective in recruiting participants will have more challenges in

their implementation, which may impair their effectiveness. For this reason, increasing the duration of training to increase its effectiveness may not be possible in everyday clinical practice. In fact, one recent study examined the feasibility of setting up a program to probe the efficacy of 40 h of cognitive training in inpatient wards (John et al., 2017). Interestingly, half of the recruited patients chose to not participate and many who agreed to participate did not complete the training, reporting that it was because they got frustrated for not getting the answers correctly or because the training was too lengthy and boring.

However, it is true that training must be intensive enough to cause significant plastic changes in the brain (Vinogradov et al., 2012). Specifically, learning a skill consists of a first phase of rapid behavioral improvements that are accompanied by only transient changes in neuronal excitability. But continuous practice leads to a second phase where behavioral improvements approach an asymptote as the brain continues its reorganization (Vinogradov et al., 2012). For instance, humans trained on a motor task show an increase in performance on the very first day of training, but activation of the motor cortex became broader for the trained task only after weeks of training (Karni et al., 1995; Sale et al., 2017). Importantly, this cortical reorganization persisted for months, suggesting the formation of stable representations after intensive training.

Finally, there is evidence that neuroplasticity may be impaired in schizophrenia. Training-induced neuroplasticity is dependent on many neuromodulators involved in arousal, attention, and reward, such as acetylcholine and glutamate (Vinogradov et al., 2012). As discussed earlier, however, there is plenty of evidence indicating that these systems are dysregulated in schizophrenia. These systemic impairments make it more difficult for patients with schizophrenia to benefit from cognitive training paradigms because they likely require a large number of training sessions. The approach proposed here would be to restore neurotransmitter imbalances while undertaking cognitive training, namely the pairing of cognitive training with pharmacological treatment in order to produce synergistic gains.

Conceivably, such an approach could increase the effectiveness of other behavioral therapies to treat schizophrenia symptoms, such as cognitive behavioral therapy and avatar therapy. In fact, evidence indicates that D-cycloserine potentiates the effects of cognitive behavioral therapy in reducing delusional beliefs in patients with schizophrenia (Gottlieb et al., 2011). However, here we focus on cognitive training for a number of reasons. First, because it is composed of repetitive, controlled and well-defined exercises, which facilitates study design and improves the replicability of findings. In addition, work done in animals has greatly advanced our understanding of the biological underpinnings of cognitive training, which will guide the combination of specific plasticity-enhancing drugs and cognitive training regimens. Finally, cognitive training is able to tackle several distinct types of deficits in schizophrenia across many levels, from very basic deficits in perceptual processes to high-level cognitive processes. In contrast, psychotherapy usually only addresses high-level abilities such as attention and reasoning, and helps to find workaround strategies. However, cognitive training might also prove valuable for psychotherapy, because cognitive deficits can significantly reduce the effectiveness of psychosocial rehabilitation (Mueser et al., 1991; Wykes et al., 2011, 1990).

5. Potential synergy between cognitive enhancers and cognitive training

Basic science studies have paved the way for manipulating neuromodulatory systems to enhance plasticity. For instance, passive tone exposure is capable of inducing plasticity if it is followed closely in time with microstimulation of the dopaminergic neurons of the ventral tegmental area, which projects to many cortical areas and signals hedonic reward (Bao et al., 2001). Additionally, pairing tone presentation with stimulation of the nucleus basalis, a hub of cholinergic efferents crucial for attention, is enough to induce plasticity of the auditory cortex (Froemke et al., 2007). Such studies highlight the potential benefit of manipulating neuromodulatory systems to produce synergistic gains when combined with behavioral approaches.

As reviewed in the preceding sections, the neurochemical abnormalities in the brains of individuals with schizophrenia span several neurotransmitter systems. Although future studies may uncover additional neurotransmitter systems altered in schizophrenia and new putative drug targets may continue to be discovered, it seems unlikely that any plasticity enhancer targeting a single neuromodulatory system will suffice to improve the range of cognitive impairments associated with schizophrenia.

Furthermore, there is substantial evidence showing distributed neural abnormalities in structural and functional neuroimaging studies (Gong et al., 2016). These macroscopic changes can potentially be caused by a variety of microscopic abnormalities including the number, volume, metabolism and arborization of neural cells. Therefore, it seems unlikely that either enhancing or inhibiting the activity of particular neural receptors will normalize neural circuits that have been dysfunctional throughout most of a patient's life.

In addition, it is important to note that most studies testing the effects of cognitive enhancers in schizophrenia have been done with already medicated, clinically stable patients. Furthermore, these patients often lack daily mental stimulation; the typical patient is unemployed, not pursuing education, and lives in social isolation. Assuming that these drugs do enhance neuroplasticity, what kind of plasticity can be expected when a patient is left in an environment lacking cognitive stimulation? We have discussed that experience-dependent plasticity in adulthood requires an appropriate context, and fortunately, there are some clinical studies that have taken advantage of this with a variety of different clinical populations.

For instance, exposure therapy is an effective treatment for post-traumatic stress disorder (Watts et al., 2013). This type of therapy consists of exposing patients to a context that resembles their particular traumatic experience (e.g. a war zone, a fire). This exposure is carried out in a safe environment, allowing patients to associate those cues with safety (extinction learning). Since one model postulates that post-traumatic stress disorder results from impaired learning, the efficacy of this therapy could be limited by one's impairment in extinction learning, even in a therapy environment (Sijbrandij et al., 2013). Conceivably, a drug that helps learning could be of use when given in a context that engages the brain in learning new contingency rules (e.g., learning that a specific context no longer poses a threat). This is the rationale for combining D-cycloserine with exposure therapy, which was found to be more effective than exposure therapy combined with placebo for patients with post-traumatic stress disorder (Difede et al., 2014). Interestingly, an analogous use of D-cycloserine has been tested for anxiety disorders (Hofmann et al., 2013). Note, however, that the effect sizes vary for different conditions and there are specific treatment moderators (McGuire et al., 2017).

Another example comes from tinnitus research, which, as discussed in section 2, arises from dysplasticity processes that include a distortion of the frequency representation in the auditory cortex. It follows, then, that a treatment capable of correcting this distortion would be of great value. Work on animals has shown that pairing the presentation of tone pips with vagus nerve stimulation, which promotes neuroplasticity by acting on the cholinergic system, results in an overrepresentation of the exposure frequency (Shetake et al., 2012), similar to what is observed in tinnitus. Based on this finding, one interesting treatment approach might be to pair vagus nerve stimulation with tone pips different from the ones overrepresented in the auditory cortex, which presumably are involved in the tinnitus perception. Indeed, a recent case report has found this approach to be clinically useful (De Ridder et al., 2015) and currently ongoing clinical trials will soon be able to confirm whether this approach significantly reduces the tinnitus percept. It is worth noting that although not directly tested in the above-mentioned case study, currently available animal data indicates that

vagus nerve stimulation alone is not effective in treating tinnitus (Engineer et al., 2013). This is another example of how therapeutic neuroplasticity could be obtained by combining neural (stimulating the vagus nerve) and cognitive/behavioral (tone pip exposure) therapeutic approaches. Moreover, it underscores the point that attempting to enhance neuroplasticity without presenting a proper therapeutic context will not result in a significant therapeutic improvement.

In sum, plasticity-enhancing drugs need to be paired with behavioral interventions to best achieve cognitive improvements. This philosophy is directly in line with a recent quote from (Keefe et al., 2011), "analogous to the need for physical exercise in an individual who takes steroids to increase muscle mass, patients with schizophrenia in cognitive enhancement trials may require learning contexts sufficient to "exercise" any newfound cognitive potential that they may have acquired from the drug under study".

5.1. How to choose the optimal drug-training combination?

A plethora of plasticity enhancers and cognitive training paradigms have been tested to date. Given the amount of time and resources needed to conduct cognitive training studies, we need to identify predictors of response to treatment and determine what types of drugs are better suited to be used in combination with different types of training. Basic and clinical studies have revealed a number of factors that should be taken into account when designing such combined interventions.

First, it is important to note the potential negative impact certain medications used in schizophrenia can have on training outcome. In particular, a range of antipsychotics has anticholinergic properties that may reduce the effectiveness of cognitive training (Vinogradov et al., 2009) or psychosocial treatments, regardless of the total antipsychotic dose (O'Reilly et al., 2016). Therefore, physicians and researchers must be mindful of the detrimental side-effects of some antipsychotics on the various neuromodulator systems, especially for long-term treatment. Moreover, anticholinergic drugs (e.g. biperiden) are sometimes prescribed to prevent or treat extrapyramidal side-effects, but their long-term use is not recommended due to a variety of side-effects that include worse cognitive function (Ogino et al., 2014). Thus, we propose that, before considering drugs to be used as adjuvants to cognitive training, efforts should be taken to discontinue anticholinergic drugs. In addition, antipsychotic maintenance treatment, particularly when using antipsychotics with strong anticholinergic effects, should adhere to the lowest effective dose strategy.

The design of these studies will also benefit from a hypothesis-driven personalized approach. In Section 3, we reviewed some of the efforts by several research groups to identify molecular biomarkers in the blood or CSF to help diagnose schizophrenia. Whereas diagnostic biomarkers are lacking (Fond et al., 2015; Weickert et al., 2013), biomarkers of treatment response have the potential to personalize and improve schizophrenia treatment (Kantrowitz, 2017; Light and Swerdlow, 2015). Below we provide examples of how we can personalize a drug and training combination based on such genetic and neurophysiologic markers.

Furthermore, the specific drug plus training combinations should take into account the individual characteristics of each patient. For instance, some studies have investigated how genetic variability might modulate the effectiveness of cognitive training. One of the most studied genes in this regard is the Catechol-O-Methyltransferase (COMT) gene, which codes for one of the major enzymes responsible for dopamine degradation in the brain. One study found that single nucleotide polymorphisms in the COMT gene could abolish cognitive gains after 50 h of cognitive training in schizophrenia (Panizzutti et al., 2013). Highlighting the complex effect of the genotype, another study found that the effect of the COMT rs4680 polymorphism on cognitive training depends on the antipsychotic taken by the patients, because Val/Val patients on clozapine had increased speed of processing after training, whereas Val/Val patients on other antipsychotics did not (Bosia et al., 2014). Moving forward, it would be important to test whether dopaminergic drugs improve the effectiveness of cognitive training in non-responders with altered dopaminergic signaling evidenced by COMT polymorphisms.

The MMN response depends on NMDAR function (Featherstone et al., 2015; Javitt et al., 1996), and is consistently found to be decreased in schizophrenia (Erickson et al., 2016). Additionally, a stronger MMN baseline measure is associated with better performance over a single 1 h-session of auditory cognitive training (Perez et al., 2017). As better training performance may indicate higher cognitive gains, a drug capable of improving MMN responses could also potentially increase cognitive gains after training.

Notably, evidence indicates that D-serine is involved in the effectiveness of cognitive training. One study observed a positive correlation between change in D-serine levels and gains in global cognition following auditory cognitive training (Panizzutti et al., submitted), which suggests that D-serine might be a useful adjuvant to cognitive training. This contrasts, however, with the findings of another study that did not show an enhancing effect of D-serine (30 mg/kg) on any cognitive domain tested (D'Souza et al., 2013). It is important to highlight, however, that the dose used in this study is lower than in a former study that showed a cognitive enhancing effect of D-serine (Kantrowitz et al., 2010). Another point to be emphasized is the low half-life of peripherally administered D-serine evidenced by in vivo brain microdialysis in mice (Guercio et al., 2014) and by human serum analysis (Kantrowitz et al., 2010), which indicates that its effectiveness might be highest if timed with the training sessions. Remarkably, the weekly administration of D-serine to patients with schizophrenia (60 mg/kg) 30 min before cognitive training sessions improves their training performance and MMN compared to training with placebo (Kantrowitz et al., 2016). Similarly, a daily dose of D-serine (60 mg/kg) has been shown to improve MMN deficits in schizophrenia (Kantrowitz et al., 2018). These studies suggest that D-serine may be used to improve the effectiveness of auditory cognitive training regimens. Future studies should assess whether D-serine combined with cognitive training improves the generalization of cognitive gains and patients' functional outcome compared to training with placebo. Because MMN correlates with general cognition and functional outcome (Biagianti et al., 2017; Perrin et al., 2018; Wynn et al., 2010), we hypothesize that D-serine may have a higher synergistic potential in patients that have larger baseline MMN deficits.

Prepulse inhibition of the startle response (PPI) can also be used to inform drug and training combinations (Chou et al., 2012). PPI is a pre-attentive, cross-species phenomenon observed when the magnitude of a startle response to a loud noise is inhibited by the presentation of a preceding weaker pulse (prepulse). The startle reflex is generated by the pons, but the prepulse causes an inhibition of the reflex by acting on several key structures including the nucleus accumbens, hippocampus, prefrontal cortex, and many others (Swerdlow et al., 2001). Importantly, PPI is thought to be a measure of sensorimotor gating, a continuously active brain process to prevent sensory overload (Swerdlow et al., 1999).

Deficits in PPI have been extensively documented in schizophrenia, and patients with higher deficits tend to have worse performance on cognitive tests and global functioning, and benefit less from cognitive training (Chou et al., 2012). Additionally, higher baseline PPI levels are associated with better responses to cognitive behavioral therapy (Kumari et al., 2012). Thus, it is tempting to speculate that drugs capable of increasing PPI in patients with schizophrenia could improve the effects of cognitive training in patients with low PPI. Notably, tolcapone is a COMT inhibitor that can improve cognition in healthy subjects depending on individual's characteristics (Bhakta et al., 2017). In schizophrenia, it enhances PPI in patients with a polymorphism associated with increased COMT activity and lower PPI levels (Giakoumaki et al., 2008).

Furthermore, amphetamine is a drug that increases dopamine release and, in a low dose of 10 mg, can improve PPI and neurocognition

in schizophrenia (Swerdlow et al., 2018). A recent study combined amphetamine with auditory discrimination training and found that training performance in the first session increased for patients with schizophrenia who took the 10 mg of the drug compared to patients in the placebo group (Swerdlow et al., 2016b). Whether this increased performance translates to a more effective transfer of cognitive gains should be assessed in future experiments, especially because there are health concerns associated with the chronic use of dopaminergic drugs by patients with schizophrenia. Perhaps a safer alternative for long-term use is to give patients 20 mg/day of memantine - a drug that targets many systems including the glutamatergic, cholinergic and dopaminergic - to improve PPI and MMN (Swerdlow et al., 2016a). In any case, the above highlighted experiments demonstrate the potential of using neurophysiological and genetic biomarkers to help determine the best individualized approach for implementing medication-enhanced cognitive training programs.

An analogous approach can be used for working memory. For instance, a PET study of the dopamine system revealed that working memory training over 5 weeks increased cortical D_1R binding in healthy participants, which correlated positively with the degree of working memory improvement after training (McNab et al., 2009). This indicates that the modulation of D_1R activity might be important for the effectiveness of working memory training. It may also indicate that, as some patients have a diminished capacity of releasing dopamine in the cortex (Slifstein et al., 2015), their ability to engage in a working memory training may benefit from a D_1R agonist.

Finally, oxytocin is a compound involved in social cognition that has been tested as an adjuvant in schizophrenia with limited success. However, one encouraging study found that 50 IU of oxytocin administered intranasally 30 min before social cognitive training sessions produced greater improvement in an empathic identification task than placebo (Davis et al., 2014a). Importantly, this drug-enhanced cognitive training effect was evident even at 1-month follow up, highlighting the beneficial effect of pairing oxytocin with social training. In contrast, another study using a smaller dose (24 IU) found no benefit of adding oxytocin to social cognitive training in young people during an early psychosis phase (Cacciotti-Saija et al., 2015). These results emphasize the need to develop a better understanding of the pharmacokinetics of oxytocin in order to determine optimal therapeutic dosage.

Because cognitive training is a time-consuming and demanding treatment, a central question is the durability of any cognitive effect found. Although some studies have described the durability of cognitive gains after cognitive training (Fisher et al., 2010; Subramaniam et al., 2014), long-term effects have not been systematically documented. All other things being equal, it is reasonable to assume that a longer training will have more durable effects. Indeed, Fisher et al. (2010) showed that a longer training period (100 h compared to 50 h) results in more durable gains in functional outcome. Importantly, in this study, patients received money for each training day, which in turn probably allowed the study to have a low dropout rate. However, as this type of treatment is incorporated into clinical practice, monetary rewards will not be available, making dropout rates for such long training periods most likely higher. Another possibility is to divide the training, giving booster sessions every 6 or 12 months. To our knowledge, no study investigating whether booster sessions can prolong the effects of cognitive training in patients with schizophrenia has been done. Remarkably, however, a recent study found that ten ~1 h training sessions designed to improve overall speed of processing in healthy older adults decreased the chance of developing dementia by 29% a decade later, and each booster session (administered at 11 and 35 months after completion of the initial training) was associated with a further 10% reduction in risk (Edwards et al., 2017). Moving forward, it will be necessary for the field to better describe the durability of any cognitive training regimen and if/when booster sessions are necessary, and whether plasticity-enhancing drugs can modify its durability.

It is important to note, however, that better performance during cognitive training does not guarantee a better transfer to other tasks. One study observed that adding D-cycloserine to an auditory discrimination task improved patients' performance on the training, but failed to increase cognitive gains on the MATRICS battery compared to the placebo training group (Cain et al., 2014). One reason for this might be that this study only trained patients on one specific task, for which a previous study had shown that large improvements did not correlate with cognitive gains on the MATRICS battery (Keefe et al., 2012).

6. Conclusion and perspectives

In summary, we have reviewed how studies using various pharmacological cognitive enhancers have demonstrated somewhat disappointing results for improving cognition in schizophrenia. Although these drugs have the potential to enhance neuroplasticity in individuals living with schizophrenia, the lack of concomitant cognitive stimulation probably undermines any meaningful therapeutic effects. Therefore, as argued above, combining these cognitive enhancers with targeted cognitive training approaches may result in more systematic improvements and lead to better outcomes (Fig. 2). Drugs may correct neurochemical imbalances that underlie neuroplasticity changes in the brain, whereas cognitive training may induce the formation of more adaptive neural circuits.

Because of the number of drugs used for cognitive enhancement and their different characteristics, we propose some potential synergistic treatment combinations for future clinical studies aiming to improve cognition in schizophrenia:

- For instance, adding a dopaminergic drug that specifically targets the D_1R, or a cholinergic drug (e.g. donepezil 5 mg/day) may facilitate working memory training. As patients see themselves progressing through the exercises more easily, they may feel rewarded and have a higher adherence to training, which in turn could improve its effectiveness. Long training regimens typically motivate patients with monetary rewards, which will not be available in a clinical setting. Whether plasticity-enhancers improve adherence to training regimens that lack an extrinsic motivator is an intriguing possibility that has been unexplored so far.
- An important consideration is the dose and timepoints in which drugs should be administered. This needs to be studied on a case-by-case basis, as drugs have a variety of pharmacokinetic and pharmacodynamic properties. Conceivably, therapeutic drug concentrations should be maintained during training and its consolidation phase (a few hours after the training session). Here we use the example of D-serine, whose properties are fairly well-known. D-serine is rapidly absorbed and has a short half-life, which indicates that its administration should be around the start of the training session. The dose of 60 mg/kg is a good starting point, as previous studies have deemed it safe and effective (for other drugs, biomarkers of target engagement, such as MMN, PPI or prefrontal cortex activity during working memory testing may be studied). Based on previous studies, D-serine should be given at least weekly, but whether daily treatment is more effective to improve cognitive training has not been directly tested. Conceivably, daily D-serine treatment could render the training regimen shorter, but again this should be investigated by future studies employing neuropsychological testing in multiple timepoints. Once training is terminated, D-serine administration should be stopped.
- Knowledge of the effects of each drug in the brain will inform specific drug and training combinations. For instance, it makes sense to use D-serine with auditory training (perceptive and higher-order), because it improves the auditory MMN response, which may be an index of auditory short-term auditory plasticity. On the other hand, a training regimen focused on working memory may benefit from dopaminergic agents, because dopamine signaling in the prefrontal cortex exerts a powerful effect on working memory. Oxytocin may induce more

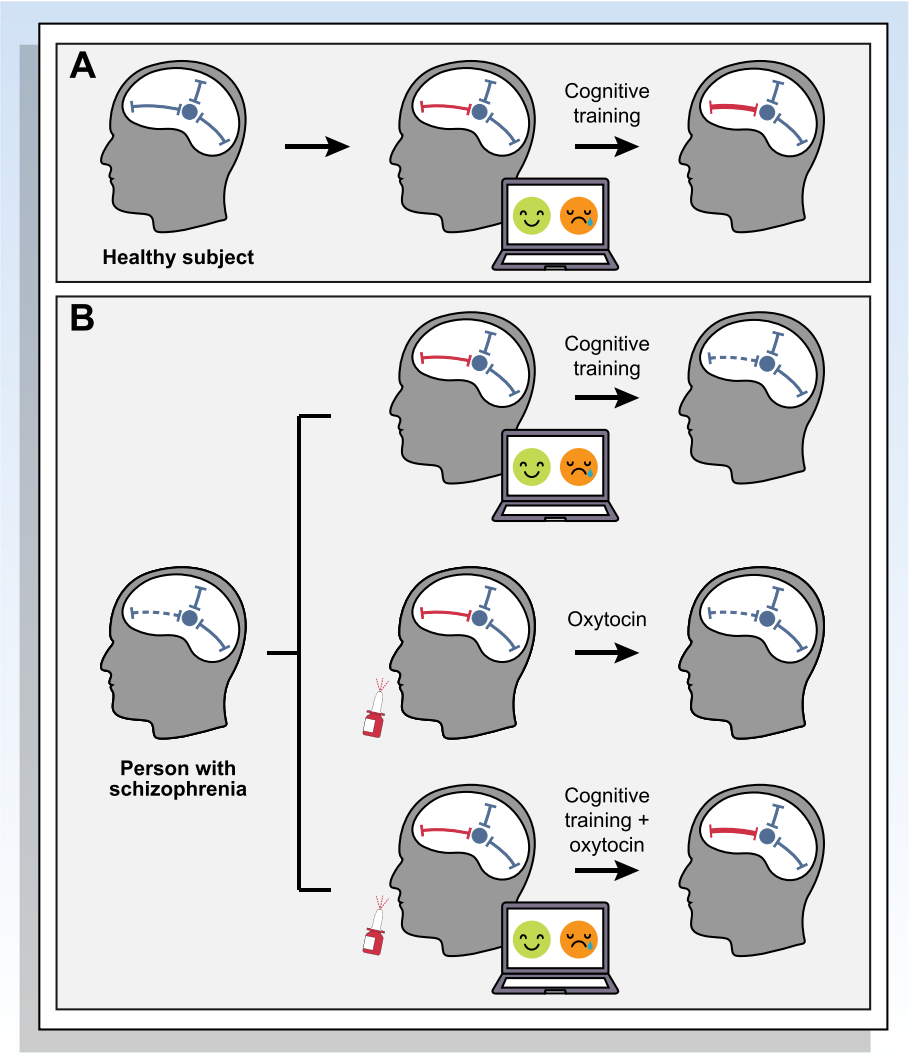

Fig. 2. Combining pharmacological treatment and cognitive training for the most effective schizophrenia treatment. A synergistic approach that pairs cognitive training with pharmacological treatment that enhances the neurological system being trained might result in the best clinical outcomes for cognitive impairment in schizophrenia. A. A healthy subject is able to improve certain aspects of social cognition through a cognitive training program that induces long-term modification of neural circuits. B. A subject with schizophrenia has pre-existing deficits in social cognition. Due to dysfunctional neuromodulatory control, treatment with cognitive training alone may take too much time and effort to produce tangible results. Similarly, drugs aimed to potentiate social cognition, such as oxytocin, are not likely to alter neural circuits in a constructive manner without the appropriate behavioral context. The combined intervention of behavioral therapy through cognitive training and administration of oxytocin could thus provide the best treatment solution.

adaptive plastic effects if tied to a training that will exercise the brain's ability to recognize emotions and understand the mental state of others.

- There is a need to identify biomarkers (molecular, genetic, neuroimaging) that predict successful transfer of cognitive effects following cognitive training. This can provide the rationale for adding specific drugs to putatively non-responder patients. For example, if cortical binding of D_1R is important for the transfer of cognitive gains to untrained tasks following working memory training, then the addition of an D_1R agonist will increase the likelihood of transfer effects after training. Future studies could assess whether this holds true specifically for patients who fail to improve PFC D_1R binding after undergoing working memory training.
- Finally, another way drugs can improve cognitive training is by prolonging its effects, which can be assessed by follow-ups months or years later. Some studies have investigated the durability of the effects of cognitive training, but as the field matures and moves into the clinic, future studies should attempt to not only describe the durability effects but also predict if/when a “boost” is needed. Presumably, the addition of plasticity-enhancing drugs concomitantly with training may induce the formation of more stable neural circuits, and so booster sessions will be further apart.

Role of funding source

The funders had no role in the preparation of the manuscript.

Contributors

G.D.G. and E.V.S. conceptualized the manuscript. G.D.G. wrote the first draft of the manuscript, with substantial input from all authors. M.T. designed the figures. All authors contributed to and have approved the final manuscript.

Conflict of interest

R.P. is the founder of NeuroForma LTDA, a company with a financial interest in cognitive training. The other authors declare no conflict of interest.

Acknowledgements

G.D.G. is a recipient of a scholarship from Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq). M.C. receives a scholarship from the Canadian Institutes for Health Research (CIHR) and M.T. receives a scholarship from the Fonds de recherche du Québec - Nature et technologies. R.P. is an Atlantic Fellow of the Global Brain Health Institute. This work is also supported by the Canadian Institutes for Health Research and the Natural Sciences and Engineering Research Council of Canada.

References

Adcock, R.A., Dale, C., Fisher, M., Aldebot, S., Genevsky, A., Simpson, G.V., Nagarajan, S., Vinogradov, S., 2009. When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia. Schizophr. Bull. 35, 1132–1141.

Amiaz, R., Kent, I., Rubinstein, K., Sela, B.A., Javitt, D., Weiser, M., 2015. Safety, tolerability and pharmacokinetics of open label sarcosine added on to anti-psychotic treatment in schizophrenia - preliminary study. Isr. J. Psychiatry Relat. Sci. 52, 12–15.

Arion, D., Corradi, J.P., Tang, S., Datta, D., Boothe, F., He, A., Cacace, A.M., Zaczek, R., Albright, C.F., Tseng, G., Lewis, D.A., 2015. Distinctive transcriptome alterations of prefrontal pyramidal neurons in schizophrenia and schizoaffective disorder. Mol. Psychiatry 20, 1397–1405.

Arnsten, A.F.T., Wang, M., Paspalas, C.D., 2015. Dopamine's actions in primate prefrontal cortex: challenges for treating cognitive disorders. Pharmacol. Rev. 67, 681–696.

Arnsten, A.F.T., Girgis, R.R., Gray, D.L., Mailman, R.B., 2017. Novel dopamine therapeutics for cognitive deficits in schizophrenia. Biol. Psychiatry 81, 67–77.

Axelsson, A., Ringdahl, A., 1989. Tinnitus—a study of its prevalence and characteristics. Br. J. Audiol. 23, 53–62.

Bakin, J.S., Weinberger, N.M., 1996. Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. Proc. Natl. Acad. Sci. U. S. A. 93, 11219–11224.

Balu, D.T., 2016. The NMDA receptor and schizophrenia: from pathophysiology to treatment. Adv. Pharmacol. 76, 351–382.

Balu, D.T., Li, Y., Puhl, M.D., Benneyworth, M.A., Basu, A.C., Takagi, S., Bolshakov, V.Y., Coyle, J.T., 2013. Multiple risk pathways for schizophrenia converge in serine racemase knockout mice, a mouse model of NMDA receptor hypofunction. Proc. Natl. Acad. Sci. U. S. A. 110, E2400–9.

Bao, S., Chan, V.T., Merzenich, M.M., 2001. Cortical remodelling induced by activity of ventral tegmental dopamine neurons. Nature 412, 79–83.

Barak, S., 2009. Modeling cholinergic aspects of schizophrenia: focus on the antimuscarinic syndrome. Behav. Brain Res. 204, 335–351.

Barr, R.S., Culhane, M.A., Jubelt, L.E., Mufti, R.S., Dyer, M.A., Weiss, A.P., Deckersbach, T., Kelly, J.F., Freudenreich, O., Goff, D.C., Evins, A.E., 2008. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. Neuropsychopharmacology 33, 480–490.

Bartz, J.A., Zaki, J., Bolger, N., Hollander, E., Ludwig, N.N., Kolevzon, A., Ochsner, K.N., 2010. Oxytocin selectively improves empathic accuracy. Psychol. Sci. 21, 1426–1428.

Bendikov, I., Nadri, C., Amar, S., Panizzutti, R., De Miranda, J., Wolosker, H., Agam, G., 2007. A CSF and postmortem brain study of D-serine metabolic parameters in schizophrenia. Schizophr. Res. 90, 41–51.

Bhakta, S.G., Light, G.A., Talledo, J.A., Balvaneda, B., Hughes, E., Alvarez, A., Rana, B.K., Young, J.W., Swerdlow, N.R., 2017. Tolcapone-enhanced neurocognition in healthy adults: neural basis and predictors. Int. J. Neuropsychopharmacol. 20, 979–987.

Biagianti, B., Roach, B.J., Fisher, M., Loewy, R., Ford, J.M., Vinogradov, S., Mathalon, D.H., 2017. Trait aspects of auditory mismatch negativity predict response to auditory training in individuals with early illness schizophrenia. Neuropsychiatr. Electrophysiol. 3, 2.

Blake, D.T., Heiser, M.A., Caywood, M., Merzenich, M.M., 2006. Experience-dependent adult cortical plasticity requires cognitive association between sensation and reward. Neuron 52, 371–381.

Bosia, M., Zanoletti, A., Spangaro, M., Buonocore, M., Bechi, M., Cocchi, F., Pirovano, A., Lorenzi, C., Bramanti, P., Smeraldi, E., Cavallaro, R., 2014. Factors affecting cognitive remediation response in schizophrenia: the role of COMT gene and antipsychotic treatment. Psychiatry Res. 217, 9–14.

Breese, C.R., Lee, M.J., Adams, C.E., Sullivan, B., Logel, J., Gillen, K.M., Marks, M.J., Collins, A.C., Leonard, S., 2000. Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. Neuropsychopharmacology 23, 351–364.

Buchanan, R.W., Conley, R.R., Dickinson, D., Ball, M.P., Feldman, S., Gold, J.M., McMahon, R.P., 2008. Galantamine for the treatment of cognitive impairments in people with schizophrenia. Am. J. Psychiatry 165, 82–89.

Bugarski-Kirola, D., Blaettler, T., Arango, C., Fleischhacker, W.W., Garibaldi, G., Wang, A., Dixon, M., Bressan, R.A., Nasrallah, H., Lawrie, S., Napieralski, J., Ochi-Lohmann, T., Reid, C., Marder, S.R., 2017. Bitopertin in negative symptoms of schizophrenia-results from the phase III FlashLyte and DayLyte studies. Biol. Psychiatry 82, 8–16.

Buonomano, D.V., Merzenich, M.M., 1998. Cortical plasticity: from synapses to maps. Annu. Rev. Neurosci. 21, 149–186.

Cacciotti-Saija, C., Langdon, R., Ward, P.B., Hickie, I.B., Scott, E.M., Naismith, S.L., Moore, L., Alvares, G.A., Redoblado Hodge, M.A., Guastella, A.J., 2015. A double-blind randomized controlled trial of oxytocin nasal spray and social cognition training for young people with early psychosis. Schizophr. Bull. 41, 483–493.

Cain, C.K., McCue, M., Bello, I., Creedon, T., Tang, D.-I., Laska, E., Goff, D.C., 2014. D-Cycloserine augmentation of cognitive remediation in schizophrenia. Schizophr. Res. 153, 177–183.

Calcia, M.A., Madeira, C., Alheira, F.V., Silva, T.C.S., Tannos, F.M., Vargas-Lopes, C., Goldenstein, N., Brasil, M.A., Ferreira, S.T., Panizzutti, R., 2012. Plasma levels of D-serine in Brazilian individuals with schizophrenia. Schizophr. Res. 142, 83–87.

Caravaggio, F., Gerretsen, P., Mar, W., Chung, J.K., Plitman, E., Nakajima, S., Kim, J., Iwata, Y., Patel, R., Chakravarty, M.M., Remington, G., Graff-Guerrero, A., Menon, M., 2017. Intranasal oxytocin does not modulate jumping to conclusions in schizophrenia: potential interactions with caudate volume and baseline social functioning. Psychoneuroendocrinology https://doi.org/10.1016/j.psyneuen.2017.03.020.

Castner, S.A., Williams, G.V., Goldman-Rakic, P.S., 2000. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. Science 287, 2020–2022.

Cavuş, I., Reinhart, R.M.G., Roach, B.J., Gueorguieva, R., Teyler, T.J., Clapp, W.C., Ford, J.M., Krystal, J.H., Mathalon, D.H., 2012. Impaired visual cortical plasticity in schizophrenia. Biol. Psychiatry 71, 512–520.

Cho, S.-E., Na, K.-S., Cho, S.-J., Kang, S.G., 2016. Low D-serine levels in schizophrenia: a systematic review and meta-analysis. Neurosci. Lett. 634, 42–51.

Chou, H.-H., Twamley, E., Swerdlow, N.R., 2012. Towards medication-enhancement of cognitive interventions in schizophrenia. Handb. Exp. Pharmacol. 81–111.

Chumakov, I., Blumenfeld, M., Guerassimenko, O., Cavarec, L., Palicio, M., Abderrahim, H., Bougueleret, L., Barry, C., Tanaka, H., La Rosa, P., Puech, A., Tahri, N., Cohen-Akenine, A., Delabrosse, S., Lissarrague, S., Picard, F.-P., Maurice, K., Essioux, L., Millasseau, P., Grel, P., Debailleul, V., Simon, A.-M., Caterina, D., Dufaure, I., Malekzadeh, K., Belova, M., Luan, J.-J., Bouillot, M., Sambucy, J.-L., Primas, G., Saumier, M., Boubkiri, N., Martin-Saumier, S., Nasroune, M., Peixoto, H., Delaye, A., Pinchot, V., Bastucci, M., Guillou, S., Chevillon, M., Sainz-Fuertes, R., Meguenni, S., Aurich-Costa, J., Cherif, D., Gimalac, A., Van Duijn, C., Gauvreau, D., Ouellette, G., Fortier, I., Raelson, J., Sherbatich, T., Riazanskaia, N., Rogaev, E., Raeymaekers, P., Aerssens, J., Konings, F., Luyten, W., Macciardi, F., Sham, P.C., Straub, R.E., Weinberger, D.R., Cohen, N., Cohen, D., Ouelette, G., Realson, J., 2002. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 99, 13675–13680.

Comoli, E., Coizet, V., Boyes, J., Bolam, J.P., Canteras, N.S., Quirk, R.H., Overton, P.G., Redgrave, P., 2003. A direct projection from superior colliculus to substantia nigra for detecting salient visual events. Nat. Neurosci. 6, 974–980.

Daskalakis, Z.J., Christensen, B.K., Fitzgerald, P.B., Chen, R., 2008. Dysfunctional neural plasticity in patients with schizophrenia. Arch. Gen. Psychiatry 65, 378–385.

Davis, M.C., Green, M.F., Lee, J., Horan, W.P., Senturk, D., Clarke, A.D., Marder, S.R., 2014a. Oxytocin-augmented social cognitive skills training in schizophrenia. Neuropsychopharmacology 39, 2070–2077.

Davis, M.C., Horan, W.P., Nurmi, E.L., Rizzo, S., Li, W., Sugar, C.A., Green, M.F., 2014b. Associations between oxytocin receptor genotypes and social cognitive performance in individuals with schizophrenia. Schizophr. Res. 159, 353–357.

De Ridder, D., Kilgard, M., Engineer, N., Vanneste, S., 2015. Placebo-controlled vagus nerve stimulation paired with tones in a patient with refractory tinnitus: a case report. Otol. Neurotol. 36, 575–580.

de Villers-Sidani, E., Alzghoul, L., Zhou, X., Simpson, K.L., Lin, R.C.S., Merzenich, M.M., 2010. Recovery of functional and structural age-related changes in the rat primary auditory cortex with operant training. Proc. Natl. Acad. Sci. U. S. A. 107, 13900–13905.

Difede, J., Cukor, J., Wyka, K., Olden, M., Hoffman, H., Lee, F.S., Altemus, M., 2014. D-Cycloserine augmentation of exposure therapy for post-traumatic stress disorder: a pilot randomized clinical trial. Neuropsychopharmacology 39, 1052–1058.

D'Souza, D.C., Radhakrishnan, R., Perry, E., Bhakta, S., Singh, N.M., Yadav, R., Abi-Saab, D., Pittman, B., Chaturvedi, S.K., Sharma, M.P., Bell, M., Andrade, C., 2013. Feasibility, safety, and efficacy of the combination of D-serine and computerized cognitive retraining in schizophrenia: an international collaborative pilot study. Neuropsychopharmacology 38, 492–503.

Edwards, J.D., Xu, H., Clark, D.O., Guey, L.T., Ross, L.A., Unverzagt, F.W., 2017. Speed of processing training results in lower risk of dementia. Alzheimers Dement. 3, 603–611.

Engineer, N.D., Møller, A.R., Kilgard, M.P., 2013. Directing neural plasticity to understand and treat tinnitus. Hear. Res. 295, 58–66.

Erickson, M.A., Ruffle, A., Gold, J.M., 2016. A meta-analysis of mismatch negativity in schizophrenia: from clinical risk to disease specificity and progression. Biol. Psychiatry 79, 980–987.

Featherstone, R.E., Shin, R., Kogan, J.H., Liang, Y., Matsumoto, M., Siegel, S.J., 2015. Mice with subtle reduction of NMDA NR1 receptor subunit expression have a selective decrease in mismatch negativity: implications for schizophrenia prodromal population. Neurobiol. Dis. 73, 289–295.

Fisher, M., Holland, C., Subramaniam, K., Vinogradov, S., 2010. Neuroplasticity-based cognitive training in schizophrenia: an interim report on the effects 6 months later. Schizophr. Bull. 36, 869–879.

Föcking, M., Lopez, L.M., English, J.A., Dicker, P., Wolff, A., Brindley, E., Wynne, K., Cagney, G., Cotter, D.R., 2015. Proteomic and genomic evidence implicates the postsynaptic density in schizophrenia. Mol. Psychiatry 20, 424–432.

Fond, G., d'Albis, M.-A., Jamain, S., Tamouza, R., Arango, C., Fleischhacker, W.W., Glenthøj, B., Leweke, M., Lewis, S., McGuire, P., Meyer-Lindenberg, A., Sommer, I.E., Winter-van Rossum, I., Kapur, S., Kahn, R.S., Rujescu, D., Leboyer, M., 2015. The promise of biological markers for treatment response in first-episode psychosis: a systematic review. Schizophr. Bull. 41, 559–573.

Forsyth, J.K., Lewis, D.A., 2017. Mapping the consequences of impaired synaptic plasticity in schizophrenia through development: an integrative model for diverse clinical features. Trends Cogn. Sci. 21, 760–778.

Froemke, R.C., Merzenich, M.M., Schreiner, C.E., 2007. A synaptic memory trace for cortical receptive field plasticity. Nature 450, 425–429.

Frydecka, D., Eissa, A.M., Hewedi, D.H., Ali, M., Drapała, J., Misiak, B., Kłosińska, E., Phillips, J.R., Moustafa, A.A., 2014. Impairments of working memory in schizophrenia and bipolar disorder: the effect of history of psychotic symptoms and different aspects of cognitive task demands. Front. Behav. Neurosci. 8, 416.

Fuchs, S.A., De Barse, M.M.J., Scheepers, F.E., Cahn, W., Dorland, L., de Sain-van der Velden, M.G., Klomp, L.W.J., Berger, R., Kahn, R.S., de Koning, T.J., 2008. Cerebrospinal fluid D-serine and glycine concentrations are unaltered and unaffected by olanzapine therapy in male schizophrenic patients. Eur. Neuropsychopharmacol. 18, 333–338.

Garey, L.J., Ong, W.Y., Patel, T.S., Kanani, M., Davis, A., Mortimer, A.M., Barnes, T.R., Hirsch, S.R., 1998. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. J. Neurol. Neurosurg. Psychiatry 65, 446–453.

Gee, K.W., Olincy, A., Kanner, R., Johnson, L., Hogenkamp, D., Harris, J., Tran, M., Edmonds, S.A., Sauer, W., Yoshimura, R., Johnstone, T., Freedman, R., 2017. First in human trial of a type I positive allosteric modulator of alpha7-nicotinic acetylcholine receptors:

pharmacokinetics, safety, and evidence for neurocognitive effect of AVL-3288. J. Psychopharmacol. 31, 434–441.
George, M.S., Molnar, C.E., Grenesko, E.L., Anderson, B., Mu, Q., Johnson, K., Nahas, Z., Knable, M., Fernandes, P., Juncos, J., Huang, X., Nichols, D.E., Mailman, R.B., 2007. A single 20 mg dose of dihydrexidine (DAR-0100), a full dopamine D1 agonist, is safe and tolerated in patients with schizophrenia. Schizophr. Res. 93, 42–50.
Giakoumaki, S.G., Roussos, P., Bitsios, P., 2008. Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism. Neuropsychopharmacology 33, 3058–3068.
Gibson, C.M., Penn, D.L., Smedley, K.L., Leserman, J., Elliott, T., Pedersen, C.A., 2014. A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia. Schizophr. Res. 156, 261–265.
Girgis, R.R., Van Snellenberg, J.X., Glass, A., Kegeles, L.S., Thompson, J.L., Wall, M., Cho, R.Y., Carter, C.S., Slifstein, M., Abi-Dargham, A., Lieberman, J.A., 2016. A proof-of-concept, randomized controlled trial of DAR-0100A, a dopamine-1 receptor agonist, for cognitive enhancement in schizophrenia. J. Psychopharmacol. 30, 428–435.
Goff, D.C., Leahy, L., Berman, I., Posever, T., Herz, L., Leon, A.C., Johnson, S.A., Lynch, G., 2001. A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. J. Clin. Psychopharmacol. 21, 484–487.
Goff, D.C., Lamberti, J.S., Leon, A.C., Green, M.F., Miller, A.L., Patel, J., Manschreck, T., Freudenreich, O., Johnson, S.A., 2008. A placebo-controlled add-on trial of the Ampakine, CX516, for cognitive deficits in schizophrenia. Neuropsychopharmacology 33, 465–472.
Goldman-Rakic, P.S., 1995. Cellular basis of working memory. Neuron 14, 477–485.
Gong, Q., Lui, S., Sweeney, J.A., 2016. A selective review of cerebral abnormalities in patients with first-episode schizophrenia before and after treatment. Am. J. Psychiatry 173, 232–243.
Gottlieb, J.D., Cather, C., Shanahan, M., Creedon, T., Macklin, E.A., Goff, D.C., 2011. D-Cycloserine facilitation of cognitive behavioral therapy for delusions in schizophrenia. Schizophr. Res. 131, 69–74.
Green, M.F., Horan, W.P., Lee, J., 2015. Social cognition in schizophrenia. Nat. Rev. Neurosci. 16, 620–631.
Guercio, G.D., Panizzutti, R., 2018. Potential and challenges for the clinical use of D-serine as a cognitive enhancer. Front. Psych. 9, 14.
Guercio, G.D., Bevictori, L., Vargas-Lopes, C., Madeira, C., Oliveira, A., Carvalho, V.F., d'Avila, J.C., Panizzutti, R., 2014. D-Serine prevents cognitive deficits induced by acute stress. Neuropharmacology 86, 1–8.
Haig, G.M., Bain, E.E., Robieson, W.Z., Baker, J.D., Othman, A.A., 2016. A randomized trial to assess the efficacy and safety of ABT-126, a selective α7 nicotinic acetylcholine receptor agonist, in the treatment of cognitive impairment in schizophrenia. Am. J. Psychiatry 173, 827–835.
Harvey, P.D., Howanitz, E., Parrella, M., White, L., Davidson, M., Mohs, R.C., Hoblyn, J., Davis, K.L., 1998. Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. Am. J. Psychiatry 155, 1080–1086.
Hashimoto, K., Fukushima, T., Shimizu, E., Komatsu, N., Watanabe, H., Shinoda, N., Nakazato, M., Kumakiri, C., Okada, S.-I., Hasegawa, H., Imai, K., Iyo, M., 2003. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the *N*-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch. Gen. Psychiatry 60, 572–576.
Hensch, T.K., 2005. Critical period plasticity in local cortical circuits. Nat. Rev. Neurosci. 6, 877–888.
Hofmann, S.G., Wu, J.Q., Boettcher, H., 2013. D-Cycloserine as an augmentation strategy for cognitive behavioral therapy of anxiety disorders. Biol. Mood Anxiety Disord. 3, 11.
Holt, D.J., Herman, M.M., Hyde, T.M., Kleinman, J.E., Sinton, C.M., German, D.C., Hersh, L.B., Graybiel, A.M., Saper, C.B., 1999. Evidence for a deficit in cholinergic interneurons in the striatum in schizophrenia. Neuroscience 94, 21–31.
Holt, D.J., Bachus, S.E., Hyde, T.M., Wittie, M., Herman, M.M., Vangel, M., Saper, C.B., Kleinman, J.E., 2005. Reduced density of cholinergic interneurons in the ventral striatum in schizophrenia: an in situ hybridization study. Biol. Psychiatry 58, 408–416.
Horan, W.P., Green, M.F., DeGroot, M., Fiske, A., Hellemann, G., Kee, K., Kern, R.S., Lee, J., Sergi, M.J., Subotnik, K.L., Sugar, C.A., Ventura, J., Nuechterlein, K.H., 2012. Social cognition in schizophrenia, part 2: 12-month stability and prediction of functional outcome in first-episode patients. Schizophr. Bull. 38, 865–872.
Jacob, S.N., Stalter, M., Nieder, A., 2016. Cell-type-specific modulation of targets and distractors by dopamine D1 receptors in primate prefrontal cortex. Nat. Commun. 7, 13218.
Javitt, D.C., Steinschneider, M., Schroeder, C.E., Arezzo, J.C., 1996. Role of cortical *N*-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 93, 11962–11967.
John, A.P., Yeak, K., Ayres, H., Dragovic, M., 2017. Successful Implementation of a Cognitive Remediation Program in Everyday Clinical Practice for Individuals Living With Schizophrenia. Educational Publishing Foundation.
Kandel, E.R., 2001. The molecular biology of memory storage: a dialogue between genes and synapses. Science 294, 1030–1038.
Kantrowitz, J.T., 2017. Managing negative symptoms of schizophrenia: how far have we come? CNS Drugs 31, 373–388.
Kantrowitz, J.T., Malhotra, A.K., Cornblatt, B., Silipo, G., Balla, A., Suckow, R.F., D'Souza, C., Saksa, J., Woods, S.W., Javitt, D.C., 2010. High dose D-serine in the treatment of schizophrenia. Schizophr. Res. 121, 125–130.
Kantrowitz, J.T., Epstein, M.L., Beggel, O., Rohrig, S., Lehrfeld, J.M., Revheim, N., Lehrfeld, N.P., Reep, J., Parker, E., Silipo, G., Ahissar, M., Javitt, D.C., 2016. Neurophysiological mechanisms of cortical plasticity impairments in schizophrenia and modulation by the NMDA receptor agonist D-serine. Brain 139, 3281–3295.
Kantrowitz, J.T., Nolan, K.A., Epstein, M.L., Lehrfeld, N., Shope, C., Petkova, E., Javitt, D.C., 2017. Neurophysiological effects of bitopertin in schizophrenia. J. Clin. Psychopharmacol. 37, 447–451.
Kantrowitz, J.T., Epstein, M.L., Lee, M., Lehrfeld, N., Nolan, K.A., Shope, C., Petkova, E., Silipo, G., Javitt, D.C., 2018. Improvement in mismatch negativity generation during D-serine treatment in schizophrenia: correlation with symptoms. Schizophr. Res. 191, 70–79.
Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turner, R., Ungerleider, L.G., 1995. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 377, 155–158.
Keefe, R.S.E., Malhotra, A.K., Meltzer, H.Y., Kane, J.M., Buchanan, R.W., Murthy, A., Sovel, M., Li, C., Goldman, R., 2008. Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology 33, 1217–1228.
Keefe, R.S.E., Vinogradov, S., Medalia, A., Silverstein, S.M., Bell, M.D., Dickinson, D., Ventura, J., Marder, S.R., Stroup, T.S., 2011. Report from the working group conference on multisite trial design for cognitive remediation in schizophrenia. Schizophr. Bull. 37, 1057–1065.
Keefe, R.S.E., Vinogradov, S., Medalia, A., Buckley, P.F., Caroff, S.N., D'Souza, D.C., Harvey, P.D., Graham, K.A., Hamer, R.M., Marder, S.M., Miller, D.D., Olson, S.J., Patel, J.K., Velligan, D., Walker, T.M., Haim, A.J., Stroup, T.S., 2012. Feasibility and pilot efficacy results from the multisite cognitive remediation in the schizophrenia trials network (CRSTN) randomized controlled trial. J. Clin. Psychiatry 73, 1016–1022.
Keefe, R.S.E., Meltzer, H.A., Dgetluck, N., Gawryl, M., Koenig, G., Moebius, H.J., Lombardo, I., Hilt, D.C., 2015. Randomized, double-blind, placebo-controlled study of encenicline, an α7 nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. Neuropsychopharmacology 40, 3053–3060.
Kew, J.N.C., Kemp, J.A., 2005. Ionotropic and metabotropic glutamate receptor structure and pharmacology. Psychopharmacology 179, 4–29.
Kilgard, M.P., Merzenich, M.M., 1998. Cortical map reorganization enabled by nucleus basalis activity. Science 279, 1714–1718.
Kitchen, H., Rofail, D., Heron, L., Sacco, P., 2012. Cognitive impairment associated with schizophrenia: a review of the humanistic burden. Adv. Ther. 29, 148–162.
Kumari, V., Postma, P., 2005. Nicotine use in schizophrenia: the self-medication hypotheses. Neurosci. Biobehav. Rev. 29, 1021–1034.
Kumari, V., Premkumar, P., Fannon, D., Aasen, I., Raghuvanshi, S., Anilkumar, A.P., Antonova, E., Peters, E.R., Kuipers, E., 2012. Sensorimotor gating and clinical outcome following cognitive behaviour therapy for psychosis. Schizophr. Res. 134, 232–238.
Labrie, V., Wong, A.H.C., Roder, J.C., 2012. Contributions of the D-serine pathway to schizophrenia. Neuropharmacology 62, 1484–1503.
Lawlor-Savage, L., Goghari, V.M., 2014. Working memory training in schizophrenia and healthy populations. Behav. Sci. 4, 301–319.
Lee, S.-W., Lee, J.-G., Lee, B.-J., Kim, Y.H., 2007. A 12-week, double-blind, placebo-controlled trial of galantamine adjunctive treatment to conventional antipsychotics for the cognitive impairments in chronic schizophrenia. Int. Clin. Psychopharmacol. 22, 63–68.
Lieberman, J.A., Dunbar, G., Segreti, A.C., Girgis, R.R., Seoane, F., Beaver, J.S., Duan, N., Hosford, D.A., 2013. A randomized exploratory trial of an α-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. Neuropsychopharmacology 38, 968–975.
Light, G.A., Swerdlow, N.R., 2015. Future clinical uses of neurophysiological biomarkers to predict and monitor treatment response for schizophrenia. Ann. N. Y. Acad. Sci. 1344, 105–119.
Lin, C.-Y., Liang, S.-Y., Chang, Y.-C., Ting, S.-Y., Kao, C.-L., Wu, Y.-H., Tsai, G.E., Lane, H.-Y., 2017. Adjunctive sarcosine plus benzoate improved cognitive function in chronic schizophrenia patients with constant clinical symptoms: a randomised, double-blind, placebo-controlled trial. World J. Biol. Psychiatry 18, 357–368.
Lindenmayer, J.-P., Khan, A., 2011. Galantamine augmentation of long-acting injectable risperidone for cognitive impairments in chronic schizophrenia. Schizophr. Res. 125, 267–277.
Lischke, A., Berger, C., Prehn, K., Heinrichs, M., Herpertz, S.C., Domes, G., 2012. Intranasal oxytocin enhances emotion recognition from dynamic facial expressions and leaves eye-gaze unaffected. Psychoneuroendocrinology 37, 475–481.
Lucas-Meunier, E., Fossier, P., Baux, G., Amar, M., 2003. Cholinergic modulation of the cortical neuronal network. Pflugers Arch. 446, 17–29.
Maletic, V., Eramo, A., Gwin, K., Offord, S.J., Duffy, R.A., 2017. The role of norepinephrine and its α-adrenergic receptors in the pathophysiology and treatment of major depressive disorder and schizophrenia: a systematic review. Front. Psych. 8, 42.
McClure, M.M., Harvey, P.D., Goodman, M., Triebwasser, J., New, A., Koenigsberg, H.W., Sprung, L.J., Flory, J.D., Siever, L.J., 2010. Pergolide treatment of cognitive deficits associated with schizotypal personality disorder: continued evidence of the importance of the dopamine system in the schizophrenia spectrum. Neuropsychopharmacology 35, 1356–1362.
McGuire, J.F., Wu, M.S., Piacentini, J., McCracken, J.T., Storch, E.A., 2017. A meta-analysis of D-cycloserine in exposure-based treatment: moderators of treatment efficacy, response, and diagnostic remission. J. Clin. Psychiatry 78, 196–206.
McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. Am. J. Psychiatry 164, 1791–1802.
McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystritsky, P., Forssberg, H., Klingberg, T., 2009. Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science 323, 800–802.
Mears, R.P., Spencer, K.M., 2012. Electrophysiological assessment of auditory stimulus-specific plasticity in schizophrenia. Biol. Psychiatry 71, 503–511.
Menning, H., Roberts, L.E., Pantev, C., 2000. Plastic changes in the auditory cortex induced by intensive frequency discrimination training. Neuroreport 11, 817–822.

Merzenich, M.M., Kaas, J.H., Wall, J., Nelson, R.J., Sur, M., Felleman, D., 1983. Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. Neuroscience 8, 33–55.
Merzenich, M.M., Nelson, R.J., Stryker, M.P., Cynader, M.S., Schoppmann, A., Zook, J.M., 1984. Somatosensory cortical map changes following digit amputation in adult monkeys. J. Comp. Neurol. 224, 591–605.
Meyer-Lindenberg, A.S., Olsen, R.K., Kohn, P.D., Brown, T., Egan, M.F., Weinberger, D.R., Berman, K.F., 2005. Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. Arch. Gen. Psychiatry 62, 379–386.
Mueser, K.T., Bellack, A.S., Douglas, M.S., Wade, J.H., 1991. Prediction of social skill acquisition in schizophrenic and major affective disorder patients from memory and symptomatology. Psychiatry Res. 37, 281–296.
Myers, C.S., Robles, O., Kakoyannis, A.N., Sherr, J.D., Avila, M.T., Blaxton, T.A., Thaker, G.K., 2004. Nicotine improves delayed recognition in schizophrenic patients. Psychopharmacology 174, 334–340.
Nahum, M., Fisher, M., Loewy, R., Poelke, G., Ventura, J., Nuechterlein, K.H., Hooker, C.I., Green, M.F., Merzenich, M., Vinogradov, S., 2014. A novel, online social cognitive training program for young adults with schizophrenia: a pilot study. Schizophr. Res. Cogn. 1, e11–e19.
Nuechterlein, K.H., Subotnik, K.L., Green, M.F., Ventura, J., Asarnow, R.F., Gitlin, M.J., Yee, C.M., Gretchen-Doorly, D., Mintz, J., 2011. Neurocognitive predictors of work outcome in recent-onset schizophrenia. Schizophr. Bull. 37 (Suppl. 2), S33–40.
Ogino, S., Miyamoto, S., Miyake, N., Yamaguchi, N., 2014. Benefits and limits of anticholinergic use in schizophrenia: focusing on its effect on cognitive function. Psychiatry Clin. Neurosci. 68, 37–49.
Okubo, Y., Suhara, T., Suzuki, K., Kobayashi, K., Inoue, O., Terasaki, O., Someya, Y., Sassa, T., Sudo, Y., Matsushima, E., Iyo, M., Tateno, Y., Toru, M., 1997. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature 385, 634–636.
O'Reilly, K., O'Connell, P., Donohoe, G., Coyle, C., O'Sullivan, D., Azvee, Z., Maddock, C., Sharma, K., Sadi, H., McMahon, M., Kennedy, H.G., 2016. Anticholinergic burden in schizophrenia and ability to benefit from psychosocial treatment programmes: a 3-year prospective cohort study. Psychol. Med. 46, 3199–3211.
Otani, S., Bai, J., Blot, K., 2015. Dopaminergic modulation of synaptic plasticity in rat prefrontal neurons. Neurosci. Bull. 31, 183–190.
Panizzutti, R., Hamilton, S.P., Vinogradov, S., 2013. Genetic correlate of cognitive training response in schizophrenia. Neuropharmacology 64, 264–267.
Papouin, T., Ladépêche, L., Ruel, J., Sacchi, S., Labasque, M., Hanini, M., Groc, L., Pollegioni, L., Mothet, J.-P., Oliet, S.H.R., 2012. Synaptic and extrasynaptic NMDA receptors are gated by different endogenous coagonists. Cell 150, 633–646.
Park, S., Holzman, P.S., 1992. Schizophrenics show spatial working memory deficits. Arch. Gen. Psychiatry 49, 975–982.
Parker, E.M., Sweet, R.A., 2017. Stereological assessments of neuronal pathology in auditory cortex in schizophrenia. Front. Neuroanat. 11, 131.
Pedersen, C.A., Gibson, C.M., Rau, S.W., Salimi, K., Smedley, K.L., Casey, R.L., Leserman, J., Jarskog, L.F., Penn, D.L., 2011. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. Schizophr. Res. 132, 50–53.
Perez, V.B., Tarasenko, M., Miyakoshi, M., Pianka, S.T., Makeig, S.D., Braff, D.L., Swerdlow, N.R., Light, G.A., 2017. Mismatch negativity is a sensitive and predictive biomarker of perceptual learning during auditory cognitive training in schizophrenia. Neuropsychopharmacology 42, 2206–2213.
Perrin, M.A., Kantrowitz, J.T., Silipo, G., Dias, E., Jabado, O., Javitt, D.C., 2018. Mismatch negativity (MMN) to spatial deviants and behavioral spatial discrimination ability in the etiology of auditory verbal hallucinations and thought disorder in schizophrenia. Schizophr. Res. 191, 140–147.
Puckett, A.C., Pandya, P.K., Moucha, R., Dai, W., Kilgard, M.P., 2007. Plasticity in the rat posterior auditory field following nucleus basalis stimulation. J. Neurophysiol. 98, 253–265.
Recanzone, G.H., Schreiner, C.E., Merzenich, M.M., 1993. Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. J. Neurosci. 13, 87–103.
Reeder, C., Harris, V., Pickles, A., Patel, A., Cella, M., Wykes, T., 2014. Does change in cognitive function predict change in costs of care for people with a schizophrenia diagnosis following cognitive remediation therapy? Schizophr. Bull. 40, 1472–1481.
Rose, D., Wykes, T., Farrier, D., Doran, A.-M., Sporle, T., Bogner, D., 2008. What do clients think of cognitive remediation therapy? A consumer-led investigation of satisfaction and side effects. Am. J. Psychiatr. Rehabil. 11, 181–204.
Rosell, D.R., Zaluda, L.C., McClure, M.M., Perez-Rodriguez, M.M., Strike, K.S., Barch, D.M., Harvey, P.D., Girgis, R.R., Hazlett, E.A., Mailman, R.B., Abi-Dargham, A., Lieberman, J.A., Siever, L.J., 2015. Effects of the D1 dopamine receptor agonist dihydrexidine (DAR-0100A) on working memory in schizotypal personality disorder. Neuropsychopharmacology 40, 446–453.
Ross, H.E., Young, L.J., 2009. Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. Front. Neuroendocrinol. 30, 534–547.
Rudolph, U., Möhler, H., 2016. Targeting cognitive deficits in schizophrenia via GABAA receptors: focus on α2, α3, and α5 receptor subtypes. The Neurobiology of Schizophrenia. Academic Press, San Diego, pp. 149–164 Chapter 9.
Sale, M.V., Reid, L.B., Cocchi, L., Pagnozzi, A.M., Rose, S.E., Mattingley, J.B., 2017. Brain changes following four weeks of unimanual motor training: evidence from behavior, neural stimulation, cortical thickness, and functional MRI. Hum. Brain Mapp. 38, 4773–4787.
Salisbury, D.F., Kuroki, N., Kasai, K., Shenton, M.E., McCarley, R.W., 2007. Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. Arch. Gen. Psychiatry 64, 521–529.
Samochocki, M., Höffle, A., Fehrenbacher, A., Jostock, R., Ludwig, J., Christner, C., Radina, M., Zerlin, M., Ullmer, C., Pereira, E.F.R., Lübbert, H., Albuquerque, E.X., Maelicke, A., 2003. Galantamine is an allosterically potentiating ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors. J. Pharmacol. Exp. Ther. 305, 1024–1036.
Sarnyai, Z., Kovács, G.L., 2014. Oxytocin in learning and addiction: from early discoveries to the present. Pharmacol. Biochem. Behav. 119, 3–9.
Sasayama, D., Hattori, K., Teraishi, T., Hori, H., Ota, M., Yoshida, S., Arima, K., Higuchi, T., Amano, N., Kunugi, H., 2012. Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. Schizophr. Res. 139, 201–206.
Schubert, M.H., Young, K.A., Hicks, P.B., 2006. Galantamine improves cognition in schizophrenic patients stabilized on risperidone. Biol. Psychiatry 60, 530–533.
Schulze, L., Lischke, A., Greif, J., Herpertz, S.C., Heinrichs, M., Domes, G., 2011. Oxytocin increases recognition of masked emotional faces. Psychoneuroendocrinology 36, 1378–1382.
Shetake, J.A., Engineer, N.D., Vrana, W.A., Wolf, J.T., Kilgard, M.P., 2012. Pairing tone trains with vagus nerve stimulation induces temporal plasticity in auditory cortex. Exp. Neurol. 233, 342–349.
Shilling, P.D., Feifel, D., 2016. Potential of oxytocin in the treatment of schizophrenia. CNS Drugs 30, 193–208.
Sijbrandij, M., Engelhard, I.M., Lommen, M.J.J., Leer, A., Baas, J.M.P., 2013. Impaired fear inhibition learning predicts the persistence of symptoms of posttraumatic stress disorder (PTSD). J. Psychiatr. Res. 47, 1991–1997.
Slifstein, M., van de Giessen, E., Van Snellenberg, J., Thompson, J.L., Narendran, R., Gil, R., Hackett, E., Girgis, R., Ojeil, N., Moore, H., D'Souza, D., Malison, R.T., Huang, Y., Lim, K., Nabulsi, N., Carson, R.E., Lieberman, J.A., Abi-Dargham, A., 2015. Deficits in prefrontal cortical and extrastriatal dopamine release in schizophrenia: a positron emission tomographic functional magnetic resonance imaging study. JAMA Psychiat. 72, 316–324.
Smith, R.C., Warner-Cohen, J., Matute, M., Butler, E., Kelly, E., Vaidhyanathaswamy, S., Khan, A., 2006. Effects of nicotine nasal spray on cognitive function in schizophrenia. Neuropsychopharmacology 31, 637–643.
Strube, W., Bunse, T., Nitsche, M.A., Wobrock, T., Aborowa, R., Misewitsch, K., Herrmann, M., Falkai, P., Hasan, A., 2015. Smoking restores impaired LTD-like plasticity in schizophrenia: a transcranial direct current stimulation study. Neuropsychopharmacology 40, 822–830.
Subramaniam, K., Luks, T.L., Fisher, M., Simpson, G.V., Nagarajan, S., Vinogradov, S., 2012. Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. Neuron 73, 842–853.
Subramaniam, K., Luks, T.L., Garrett, C., Chung, C., Fisher, M., Nagarajan, S., Vinogradov, S., 2014. Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. NeuroImage 99, 281–292.
Švob Štrac, D., Pivac, N., Mück-Šeler, D., 2016. The serotonergic system and cognitive function. Transl. Neurosci. 7, 35–49.
Swerdlow, N.R., 2012. Beyond antipsychotics: pharmacologically-augmented cognitive therapies (PACTs) for schizophrenia. Neuropsychopharmacology 37, 310–311.
Swerdlow, N.R., Braff, D.L., Geyer, M.A., 1999. Cross-species studies of sensorimotor gating of the startle reflex. Ann. N. Y. Acad. Sci. 877, 202–216.
Swerdlow, N.R., Geyer, M.A., Braff, D.L., 2001. Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. Psychopharmacology 156, 194–215.
Swerdlow, N.R., Bhakta, S., Chou, H.-H., Talledo, J.A., Balvaneda, B., Light, G.A., 2016a. Memantine effects on sensorimotor gating and mismatch negativity in patients with chronic psychosis. Neuropsychopharmacology 41, 419–430.
Swerdlow, N.R., Tarasenko, M., Bhakta, S.G., Talledo, J., Alvarez, A.I., Hughes, E.L., Rana, B., Vinogradov, S., Light, G.A., 2016b. Amphetamine enhances gains in auditory discrimination training in adult schizophrenia patients. Schizophr. Bull. https://doi.org/10.1093/schbul/sbw148.
Swerdlow, N.R., Bhakta, S.G., Talledo, J.A., Franz, D.M., Hughes, E.L., Rana, B.K., Light, G.A., 2018. Effects of amphetamine on sensorimotor gating and neurocognition in antipsychotic-medicated schizophrenia patients. Neuropsychopharmacology 43, 708–717.
Tsai, G., Lane, H.-Y., Yang, P., Chong, M.-Y., Lange, N., 2004. Glycine transporter I inhibitor, *N*-methylglycine (sarcosine), added to antipsychotics for the treatment of schizophrenia. Biol. Psychiatry 55, 452–456.
Vijayraghavan, S., Wang, M., Birnbaum, S.G., Williams, G.V., Arnsten, A.F.T., 2007. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat. Neurosci. 10, 376–384.
Vinogradov, S., Nagarajan, S., 2017. Association of sensory processing with higher-order cognition and functioning in schizophrenia: mapping the world. JAMA Psychiat. 74, 17–18.
Vinogradov, S., Fisher, M., Warm, H., Holland, C., Kirshner, M.A., Pollock, B.G., 2009. The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. Am. J. Psychiatry 166, 1055–1062.
Vinogradov, S., Fisher, M., de Villers-Sidani, E., 2012. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology 37, 43–76.
Voss, P., Thomas, M., Chou, Y.C., Cisneros-Franco, J. Miguel, Ouellet, L., de Villers-Sidani, E., 2016. Pairing cholinergic enhancement with perceptual training promotes recovery of age-related changes in rat primary auditory cortex. Neural Plast.:2016 https://doi.org/10.1155/2016/1801979.
Voss, P., Thomas, M.E., Cisneros-Franco, J.M., de Villers-Sidani, É., 2017. Dynamic brains and the changing rules of neuroplasticity: implications for learning and recovery. Front. Psychol. 8, 1657.
Walling, D., Marder, S.R., Kane, J., Fleischhacker, W.W., Keefe, R.S.E., Hosford, D.A., Dvergsten, C., Segreti, A.C., Beaver, J.S., Toler, S.M., Jett, J.E., Dunbar, G.C., 2016.

Phase 2 trial of an alpha-7 nicotinic receptor agonist (TC-5619) in negative and cognitive symptoms of schizophrenia. Schizophr. Bull. 42, 335–343.
Watts, B.V., Schnurr, P.P., Mayo, L., Young-Xu, Y., Weeks, W.B., Friedman, M.J., 2013. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. J. Clin. Psychiatry 74, e541–50.
Weickert, C.S., Weickert, T.W., Pillai, A., Buckley, P.F., 2013. Biomarkers in schizophrenia: a brief conceptual consideration. Dis. Markers 35, 3–9.
Woolley, J.D., Chuang, B., Lam, O., Lai, W., O'Donovan, A., Rankin, K.P., Mathalon, D.H., Vinogradov, S., 2014. Oxytocin administration enhances controlled social cognition in patients with schizophrenia. Psychoneuroendocrinology 47, 116–125.
Wykes, T., Sturt, E., Katz, R., 1990. The prediction of rehabilitative success after three years. The use of social, symptom and cognitive variables. Br. J. Psychiatry 157, 865–870.
Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatry 168, 472–485.
Wykes, T., Reeder, C., Huddy, V., Taylor, R., Wood, H., Ghirasim, N., Kontis, D., Landau, S., 2012. Developing models of how cognitive improvements change functioning: mediation, moderation and moderated mediation. Schizophr. Res. 138, 88–93.
Wynn, J.K., Sugar, C., Horan, W.P., Kern, R., Green, M.F., 2010. Mismatch negativity, social cognition, and functioning in schizophrenia patients. Biol. Psychiatry 67, 940–947.
Zhu, W., Zhang, Z., Qi, J., Liu, F., Chen, J., Zhao, J., Guo, X., 2014. Adjunctive treatment for cognitive impairment in patients with chronic schizophrenia: a double-blind, placebo-controlled study. Neuropsychiatr. Dis. Treat. 10, 1317–1323.