

## **Recent Developments in Treating Cognitive Impairment Associated with Schizophrenia**

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## **ABSTRACT**

Pervasive and wide-ranging cognitive deficits are a core feature of schizophrenia and an important determinant of long-term functional outcome. The lack of sufficiently effective treatments for cognitive impairment associated with schizophrenia (CIAS) represents a major unmet need and a central roadblock towards recovery. This is partly due to the current therapeutic focus on clinical symptoms, and the relative neglect of cognitive impairments despite their functionally disabling effects. Furthermore, effective treatment is impeded by our limited knowledge of the complex pathophysiology, which gives rise to perturbed information processing. Here, we review mechanisms and effectiveness of available pharmacological and non-pharmacological treatments for CIAS. Current evidence indicates, that while techniques which broadly enhance neural plasticity show the greatest therapeutic potential, effect sizes are at best moderate. Among other reasons, this is due to a considerable heterogeneity of responses to individual interventions. Furthermore, we discuss how recent conceptual advances in operationalizing cognitive impairments based on cognitive neuroscience have the potential to address these issues and facilitate the development of novel treatment strategies for CIAS. This includes more clearly elucidating pathophysiological mechanisms in both humans and animal models, identifying new treatment targets as well as establishing biomarkers for a better prediction of treatment responses.

## **KEYWORDS**

Schizophrenia, cognitive dysfunction, neural plasticity, inflammation, cognitive imaging biomarker, pharmacological treatment, cognitive remediation, aerobic exercise, brain stimulation

## Introduction

“I have no common thread in my thinking. I take so much information into my consciousness, but I cannot process it. I cannot structure the whole flood of information, which is in my head, and sort it according to importance. Dividing a task into small individual steps and then working through them in a structured manner is sometimes an impossibility. I have a hard time focusing. I was preparing a presentation with my fellow students and my head would just shut down again and again.”

These words by a patient suffering from schizophrenia succinctly summarize the considerable functional burden resulting from the wide-ranging and pervasive cognitive disturbances, which constitute a central feature of the disorder. Currently, the lack of broadly effective and durable treatment options for CIAS constitutes one of the greatest therapeutic challenges and a major unmet need [1-3]. In this review we summarize recent conceptual advances aiming to reduce translational obstacles on the way towards addressing this important issue. We examine current efforts to expand both pharmacological and non-pharmacological cognitive enhancement approaches and discuss mechanistic similarities. Finally, we outline important areas for future research, which should facilitate the development of novel and more effective pro-cognitive interventions.

## Section I: Schizophrenia – a disorder of impaired information processing

### *The cognitive phenotype*

On average, patients with schizophrenia consistently score about two standard deviations lower than healthy controls in a wide variety of cognitive domains including attention, executive function, verbal fluency, working and long-term memory [4-12].

Indeed, schizophrenia is first and foremost an information processing disorder [13-16]. Largely due to this characteristic, it is one of the potentially most severe and chronic forms of mental illness, which consistently ranks among the top ten most frequent causes of disability in developed countries [17]. Yet, the current diagnostic criteria of schizophrenia continue to emphasize almost exclusively its clinical symptom dimensions [18,19], which comprise positive symptoms such as hallucinations and delusions, negative symptoms like anhedonia, avolition and social withdrawal as well as thought disorder but do not include concomitant cognitive deficits. This omission of cognitive dysfunction is a key factor contributing to its relative disregard in routine treatment efforts [1,18,20]. The inclusion of a cognitive impairment qualifier for schizophrenia in ICD-11 is a first tentative step toward addressing this issue. It will require clinicians to rate the global degree of cognitive deficits along with other symptom dimensions [21].

Importantly, despite its severity and contrary to early conceptual critiques [22], cognitive dysfunction does not result from a global, generalized cognitive deficit [23,24] or an overall reduction in intelligence [25]. This is underscored by evidence for areas of preserved cognitive function [24], whose delineation requires sufficiently refined cognitive models and experimental paradigms [23].

### *The dysconnection syndrome*

Schizophrenia has a clear neurodevelopmental background with a pathophysiological trajectory spanning multiple decades [26]. Compared to other neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) it has a late onset typically during adolescence or early adulthood [27]. Illness onset is preceded by multiple “hits” triggering

pathophysiological cascades at several crucial stages of brain development [26,28]. There is converging evidence that these processes lead to the emergence of a widespread dysconnection syndrome [29,30], which results in increasing cognitive impairment. Widespread dysconnection on the micro- and macrocircuit level is also a parsimonious explanation for most findings in the vast functional neuroimaging literature on the neurophysiological basis of impaired information processing in schizophrenia [31]. Although a more detailed account of this literature is beyond the scope of this review, this should by no means diminish the vital importance of functional neuroimaging for this field of research.

One central mechanism underlying this dysconnection syndrome appears to be synaptic dysfunction [32]. There is evidence for an enrichment of schizophrenia risk variants in genes related to synaptic function [33-37]. Furthermore, post-mortem studies have also consistently reported synaptic abnormalities [33,38]. An important consequence of synaptic dysfunction are disturbances of synaptic plasticity and other aspects of neural plasticity, which likely contribute to cortical microcircuit dysfunction [38-40]. Together, these mechanisms are widely considered to be a central pathophysiological pathway of schizophrenia and a major point of pathophysiological convergence [41,42].

### *E/I imbalance*

Recently, one central aspect of microcircuit dysfunction has emerged as an important research focus. Computation in the brain relies crucially on the interplay of cortical excitatory pyramidal cells and inhibitory interneurons, which sets a ratio of excitation and inhibition (E/I balance). Reciprocal excitatory-inhibitory microcircuits are essential for the generation of neural oscillations in the gamma frequency range (~30

- 200 HZ) [43]. Gamma oscillations play an important role for a many key cognitive functions including perception, attention, working memory and executive control [44-47]. A growing body of evidence of attenuated gamma oscillations in schizophrenia engaged in a variety of cognitive tasks supports the notion that disturbances of gamma oscillations are a major pathophysiological mechanism contributing to CIAS [48-50]. Importantly, a disruption of E/I balance appears to be an important factor underlying disturbed gamma oscillations [51]. Specifically, the break in E/I balance in schizophrenia has been attributed to neurobiological alterations and functional abnormalities of cortical GABAergic inhibitory interneurons [51,52]. Among the different classes of GABAergic interneurons, parvalbumin (PV) expressing neurons have most consistently been implicated [53,54]. PV neurons are recruited by phasic NMDA receptor mediated input from pyramidal neurons and provide recurrent GABA-A  $\alpha 1$  receptor mediated perisomatic inhibitory feedback [55,56]. Recurrent inhibition of excitatory pyramidal cells by PV neurons is a central element of excitatory-inhibitory loops. Importantly, the causal role of PV neurons and other subclasses of interneurons for the generation of high-frequency oscillations has been firmly established by optogenetic experiments [57,58]. Abnormalities in PV neurons in schizophrenia include lower messenger RNA and protein levels of the glutamic acid decarboxylase 67 kD isoform (GAD67), a main GABA synthesizing enzyme [52]. Conversely, cortical PV neuron density appears to be unaltered [52]. As a consequence of decreased GAD67 levels in PV neuron terminals inhibitory inputs onto pyramidal neurons are likely reduced, contributing to E/I imbalance. These changes appear to form the neurobiological basis for a decreased power of gamma oscillation in schizophrenia [52]. Together, these findings underscore the significance of the altered E/I balance

and disturbed neural oscillations for understanding the pathophysiology of CIAS and also provide important clues for novel therapeutic avenues [59].

### *The neurodevelopmental gradient hypothesis*

Schizophrenia is not the only neurodevelopmental disorder with a late onset. Based on converging neuroimaging and genetic evidence of considerable overlap between clinical and especially cognitive symptoms, there appears to be a connection between schizophrenia and bipolar disorder [60], with bipolar disorder having seemingly less neurodevelopmental anomalies connecting with higher functional capacity [61]. Similarly, first episode patients with bipolar disorder have similar but less severe deficits in neurocognition as compared to first episode patients with schizophrenia [62] despite normal pre-morbid cognitive functioning. These findings demonstrate that cognitive deficits in mental disorders are not exclusive to schizophrenia. Furthermore, findings from genetic studies have led to the conceptualization of a neurodevelopmental gradient [63]. Accordingly, the gradient of increasing neurodevelopmental and cognitive impairment starts with bipolar disorder having the least impairment, followed by ADHD, schizophrenia, ASD, and intellectual disability [64].

In line with the neurodevelopmental origin of schizophrenia, subtle cognitive deficits can already be detected in children of patients during early adolescence [65]. The first clear indications of cognitive dysfunction can typically be observed during the prodromal phase [66-69] and prior to the manifestation of the first clinical symptoms [70-72]. The largest degree of cognitive decline appears to occur during the early stages of illness before the first full-blown psychotic episode and the initiation of antipsychotic treatment [73,74], leading to a largely stable deficit throughout



subsequent illness phases [75,76]. Thus, cognitive deficits cannot be considered being a consequence of psychopharmacological interventions. Notably, cognitive deficits are also present in patients with schizophrenia spectrum disorders to a lesser degree [77,78]. Subtle disturbance of information processing can also be observed in patients' siblings, especially in first-degree relatives [79-82]. However, cognitive impairment is clearly linked to firmly established common and rare genetic variants conferring risk to schizophrenia [83-87].

The clear link to the emerging genetic architecture, the early onset years before any other overt signs of mental illness, the presence in unaffected relatives and the persistence over the course of the illness independent of medication status [88] clearly indicate that cognitive impairments are not secondary sequelae of the disorder. Rather, they are now widely regarded as a direct consequence of abnormal brain function and a primary correlate of the pathophysiology of schizophrenia [16,29,89].

This conceptual shift is not limited to schizophrenia but applies to most major psychiatric disorders [90]. Accordingly, it is also the basis of the research domain criteria (RDoC) initiative, which was launched by the National Institute of Mental Health (NIMH) in order to characterize mental disorders based on biological mechanisms, rather than the traditional clinically operationalized diagnostic categories [91]. The dimensional RDoC framework is founded on three major premises: mental illnesses can be conceptualized as brain disorders, clinical neuroscience measurements can reliably assess the underlying neural circuit dysfunction, and genetic and clinical neuroscience data can generate "biosignatures" across conventional diagnostic boundaries that lead to considerable improvements in uncovering basic neurobiological mechanisms and hence diagnosis and treatment of mental disorders [92,93]. Accordingly, essential cognitive systems comprising the constructs perception,

attention, working memory, cognitive control, declarative memory as well as language are a crucial element of the RDoC matrix. This highlights their importance for brain-circuit-based conceptualizations of mental disorders and should also facilitate a greater focus on treating cognitive dysfunction.

### *The functional consequences of cognitive dysfunction*

The necessity for a change of focus from clinical to cognitive symptoms in the treatment of schizophrenia is underscored by the lack of a correlation between psychotic symptoms and functional outcome [94]. In fact, the treatment of positive symptoms does not seem to improve cognitive deficits to a relevant degree [95]. Conversely, a clear connection has been demonstrated between current cognitive deficits and later levels of community functioning, which strongly depends on patients' general functional capacity [2,96].

Cognitive deficits strongly affect key aspects of patients' life including social relationships, living independently and employment [1,97,98], severely impeding their ability to return into successful lives. Furthermore, the diagnosis of schizophrenia is correlated to high incidence rates of homelessness [99,100]. These factors contribute substantially to the enormous societal impact and indirect costs of schizophrenia [101]. This significant societal cost of schizophrenia pose a heavy economic burden of healthcare costs and productivity loss [102]. The toll on patients is also reflected by reduced reproductive and marital rates [103].

Importantly, the degree of cognitive impairment is a strong indicator of occupational functioning with more deficits correlating with less employment [104]. With more employment success, patients are able to live independently, significantly increasing their quality of life [105,106]. Accordingly, vocational rehabilitation programs

with supported employment show effectiveness in employment rates and improvements in cognition [107-109]. Overall, the close relationship between cognition and long-term functional outcome is possibly the single most important rationale for treating cognitive dysfunction [2] (Figure 1).

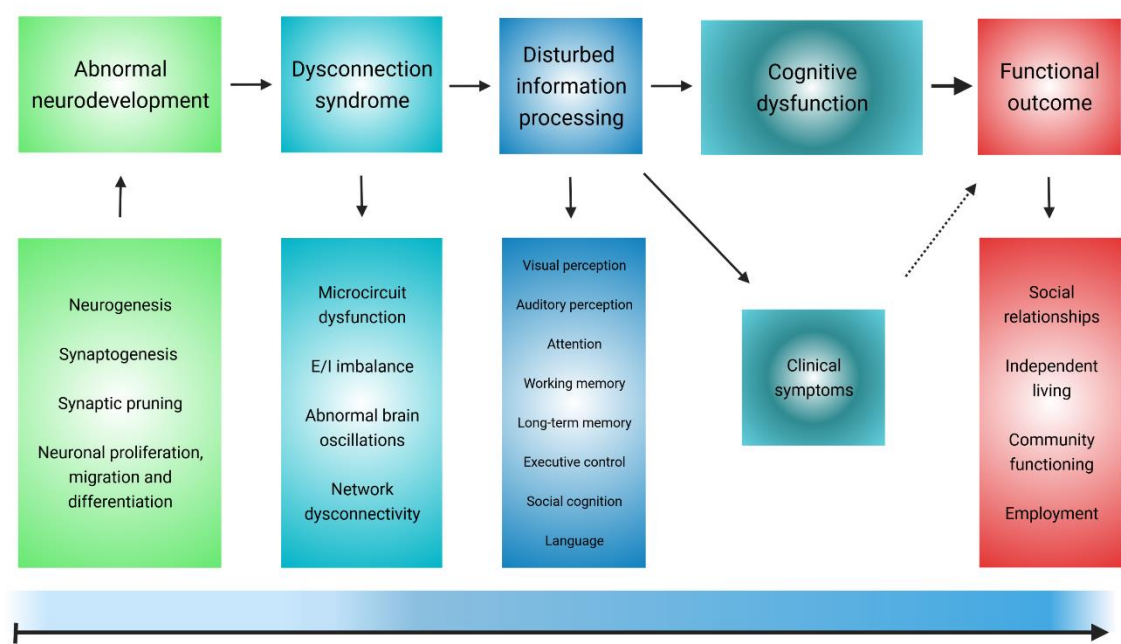


Figure 1

**Figure 1: Cognitive dysfunction and the pathophysiology of schizophrenia**

Schizophrenia is a neurodevelopmental disorder leading to a dysconnection syndrome and inducing disturbed information processing. Impaired information processing is the basis of both cognitive dysfunction and clinical symptoms. With respect to patients' functional outcome cognitive dysfunction is of particular relevance.

*Operationalizing and assessing cognitive dysfunction*

Important prerequisites for treating cognitive deficits are the definition and operationalization of relevant cognitive domains and the possibility of their reliable and repeated assessment in patient populations. An important concerted effort in this direction was the “Measurement and Treatment Research to Improve Cognition in Schizophrenia” (MATRICS) initiative. It resulted in the creation of the MATRICS cognitive consensus battery (MCCB), a battery of cognitive tasks for the explicit purpose of evaluating the effectiveness of pharmacological and non-pharmacological cognitive enhancement interventions [110]. It includes ten tests probing seven distinct cognitive domains: speed of processing, attention/vigilance, working memory, verbal and visual learning, reasoning and problem solving as well as social cognition. Thus, MATRICS also provided a widely accepted framework of cognitive constructs in order to achieve greater harmonization of research in this field. Yet, MATRICS drew mainly upon tasks from clinical neuropsychology.

Conversely, the “Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia” [111-113] initiative – while building on MATRICS – followed a translational research strategy primarily informed by basic cognitive neuroscience. It utilized concepts and constructs firmly established by cognitive neuroscience to study brain systems closely involved in crucial cognitive processes with the goal of identifying mechanisms, which could improve their function in schizophrenia [114]. To this end, CNTRICS aimed to encompass both research in animal models as well as psychophysical and functional neuroimaging research in healthy cohorts and patients. The cognitive domains and constructs deemed to have the greatest translational potential were visual perception, working memory, attention, executive control, long-term memory, and social cognition.

The design and selection process for cognitive tasks probing these domains for use in future clinical trials followed a number of evaluation criteria. These comprised good construct validity and psychometric characteristics, correlation with functional outcome, clear links to neural systems, neuropsychopharmacology and cognitive mechanisms, good suitability for human neuroimaging studies and availability of animal models [115]. The last criterion was motivated by the parallel initiative to further develop comparable tasks for rodent models [116].

The subsequent and still ongoing “Cognitive Neuroscience Test Reliability And Clinical applications for Schizophrenia” (CNTRACS) initiative continued the evaluation and optimization of the most promising tasks for use in clinical settings and as potential endpoints for treatment development research [117,118]. Importantly, the overall research strategy underlying MATRICS, CNTRICS and CNTRACS provides a detailed blueprint for the systematic translational investigation of cognitive impairments for cognitive domains and disorders beyond the original scope of these initiatives.

### *Central cognitive deficits in schizophrenia*

While CNTRICS focused on cognitive constructs with the greatest immediate translational potential, this selection is by no means exclusive. The following section provides an overview over important aspects of the most important cognitive domains, which to our view also include auditory perception and language function (Figure 2).

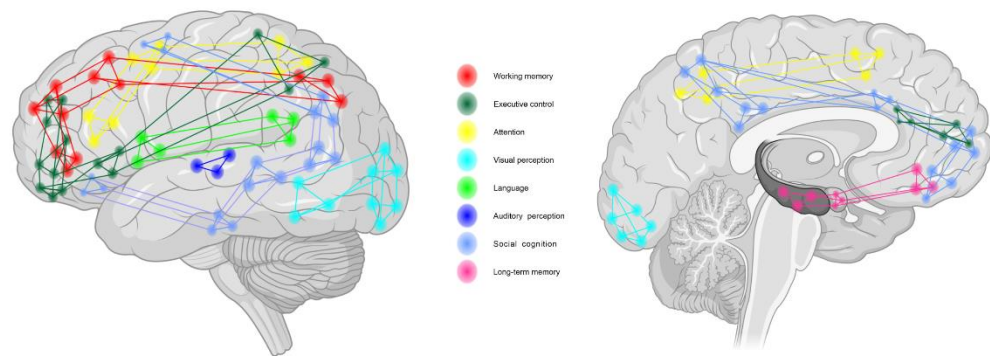


Figure 2

### Figure 2: Central cognitive domains impaired in schizophrenia

Cognitive dysfunction emerges from disturbed information processing and affects a number of key cognitive domains, whose underlying cerebral networks are disturbed by the dysconnection syndrome.

#### Visual perception

The profoundness of impaired information processing in schizophrenia is perhaps best exemplified by basic perceptual disturbances. Visual impairments have been extensively characterized at multiple processing levels [119,120]. They include early deficits in visual acuity and contrast sensitivity as well as impairments in numerous facets of perceptual organization such as spatial and object discrimination.

Disturbed perceptual organization reflects an intermediate level impairment, which encompasses aberrant processing in both the ventral and dorsal visual pathways [121-125]. Ventral and dorsal visual stream dysfunction in turn contributes

to perturbed processing in subsequent cognitive nodes such as the prefrontal cortex (PFC).

Downstream effects of aberrant visual processing can therefore impact higher-order cognitive functions that are dependent on perceptual information, including object recognition [121,124], social cognition [126,127] and working memory [128,129]. Moreover, visual distortions and difficulties in merging visual inputs into a coherent percept contribute to visual hallucinations [120,130-132]. Living with such abnormal visual representations and their consequences thus appears to be related to both cognitive deficits as well as the emergence of psychotic symptoms.

### Auditory perception

Similar to visual dysfunction, patients with schizophrenia also experience deficits in the auditory domain, which encompass multiple levels of processing and can have downstream cognitive, psychosocial and clinical consequences [119]. That is, effects of aberrant auditory processing range from issues during every-day social interactions to auditory-verbal hallucinations [133]. They primarily emerge from auditory cortex dysfunction linked to imprecise basic auditory processing such as tonal discrimination [134-136]. Consequently, patients with schizophrenia may experience difficulties in extracting relevant information [137]. This in turn promotes delusional thinking and auditory hallucinations [138-143]. Along with its clinical implications, auditory dysfunction has fundamental consequences for psychosocial functioning [119]. Impaired processing of prosodic information during social interactions impedes the perception of context beyond semantic information, such as emotional and attitudinal tone and emphasis of words. An inability to detect prosodic information, indicating e.g. sarcasm or sadness, hinders functional social interactions and thus

negatively impacts social and role function [133]. Therefore, it constitutes a central mechanism by which auditory dysfunction and consequential processing deficits affect daily functioning in schizophrenia.

### Attention

The term attention refers to the ability to select information to be focused on and eventually stored in memory or used for other higher cognitive processes. As multiple items compete for limited processing in visual attention, the dynamic interplay of selecting relevant and ignoring irrelevant information is crucial for the successful control of attention [144,145]. The control of attention appears to be specifically disturbed in schizophrenia, i.e., the endogenous guidance of attention to specific items, which is distinct from the actual implementation of selection [146]. For instance, patients require more time to guide attention to target stimuli in an array of similar objects [147].

Furthermore, patients have an attentional bias toward highly salient information [148], which can have both positive [149] and negative cognitive consequences [148] depending of the relevance of this information. In this context, it is also important to note that attending to irrelevant information and adding significance to such stimuli is an essential mechanism underlying delusions and other positive symptoms [150,151]. This attribution of abnormal salience appears to be caused primarily by disturbances of mesolimbic dopaminergic neurotransmission, which form the final common pathway of psychosis [152]. Yet, this phenomenon also demonstrates the close connection between abnormal attentional processing and the clinical symptoms of schizophrenia.

However, not all components of attention are affected in schizophrenia. In addition to the implementation of attentional selection, the ability to ignore visual distractors is



intact, as well as input selection, and the fast allocation of attention [149,153,154]. The use of exogenous cues to guide attention also appears to be intact [155].

### Working Memory

Working memory is a sub-process of short-term memory and allows to hold in information temporarily accessible for further cognitive operations. It is considered to be an essential determinant of cognitive functioning [156], and is a crucial mediator of cognitive development and learning [157,158]. Working memory deficits in patients with schizophrenia have been reported across all stages of the illness [148,149,159-164], including the prodromal phase [165,166].

Working memory comprises three essential component processes, the encoding, maintenance and retrieval of information. Psychophysical and neurophysiological evidence indicates that the encoding phase is primarily impaired in schizophrenia [49,128,129,167]. The component process model of working memory dysfunction is especially relevant because of the differential dopaminergic modulation of these processes in the PFC [168,169]. Furthermore, the consolidation of information in working memory also appears to be disturbed [164]. However, other aspects of working memory seem to be preserved, including successfully removing irrelevant information from memory, and the utilization of top-down and bottom-up visual cues to select information to be encoded [170,171]. In addition to data indicative of an overall reduction of working capacity in terms of the number of stored items [172] there is also clear evidence for a reduced precision of working memory representations [173]. Reduced working memory capacity is a robust predictor of general cognitive as well as functional impairment [172,174]. These findings indicate that improving working

memory dysfunction should have wide-ranging pro-cognitive and pro-functional effects.

### Long-term memory

Long-term memory in schizophrenia is disturbed on multiple levels, showing possibly the largest effect sizes among cognitive impairments [175]. The most pronounced deficits have been observed in episodic memory, a substrate of declarative memory responsible for recalling specific events [175,176]. Converging evidence points to specific memory deficits in schizophrenia, which limit deep encoding into episodic memory under high levels of processing demand [177-180]. Specifically, relational encoding is clearly compromised, while item-specific encoding is relatively unimpaired. More automatic learning and memory mechanisms also appear to be mostly intact [178]. Conversely, conscious recollection and autobiographical memory have also seem to be disturbed [181]. Impairments in another important substrate of declarative memory, semantic memory, have also been repeatedly demonstrated [182].

Notably, there is also evidence that working memory and long term memory are tightly intertwined. Successful long-term memory encoding and retrieval depends upon efficient control of information processing during working memory [183]. It has also been demonstrated that these interactions between working and long-term memory are disrupted in schizophrenia [184]. This indicates that working memory dysfunction might contribute to long-term memory deficits and that these might be improved by ameliorating working memory impairments.

### Executive functioning

Deficits in executive control seem to be more prominent in schizophrenia than in other psychiatric disorders [185]. They have been reported across all phases of the illness as well as in high risk individuals and first degree relatives [186,187]. Traditionally, a number of core executive control processes have been defined including updating (information updating and monitoring), inhibition (of prepotent responses), shifting (mental set shifting) and divided attention (coordinating dual tasks) [188]. Deficits in schizophrenia have been reported across all four domains of executive function [187,189]. Furthermore, rule generation and selection – processes crucial for using endogenous or exogenous cues to activate task-related goals or rules and actively representing and maintaining them in a highly accessible state in order to bias and constrain attention and response selection – has been implicated as an essential executive control deficit in schizophrenia [190,191]. Dynamic adjustments in control – processes crucial for detecting conflict or errors in ongoing processing, identifying the required type of control adjustments and recruiting additional control processes – have similarly been implicated [190,191].

Executive function is clearly linked to functional outcome [192], and independent living in patients [193]. Impaired executive functioning has been specifically connected to poorer functional outcome due to lack of illness insight and lower medication adherence [193]. Also, higher ratings of positive and negative symptoms tend to correlate with executive function deficits [194].

### Social cognition

Patients with schizophrenia experience difficulties performing mental operations required for perceiving, interpreting and reacting to social information [195,196]. These deficits are thought to arise from cascades of disturbed information processing

streams. There is evidence for impairments related to bottom-up processing, including processing of speech prosody [197-199] and facial expressions [119,200-207]. Furthermore top-down components such as attentional control and expectation biases [119,208] are also affected. As a consequence, they impede societal integration, promote social withdrawal [196] and also contribute to paranoid thinking through misinterpretation of the social intent of others [209,210].

Impaired social cognition itself constitutes a major predictor of poor functional outcome in schizophrenia [211]. However, it also acts as a mediator, such that neurocognitive deficits to a large degree exert their deleterious effect on daily functioning through their impact on social cognition [212-216]. Yet, not all sub-processes of social cognition are equally affected. An influential conceptualization [217] proposes that social cognitive deficits are primarily observed in reflective social processes which require active cognitive engagement, i.e. mental state attribution, emotion regulation and social cue perception. Conversely, reflexive social processes such as experience sharing and emotion experience, which require less mental processing, appear to be largely intact [218,219].

### Language

Difficulties during social interactions are not only the result of social cognitive deficits but are also promoted by altered use of language in patients with schizophrenia. Due to disorganized speech and auditory-linguistic hallucinations, disturbed language production and language processing also pose a prominent clinical issue [18]. Language abnormalities can reflect both aberrant linguistic processing as a distinct domain as well as the expression of disordered thought in speech [220-222]. Similar to other clinical symptoms, language abnormalities can be classified into

positive language symptoms such as neologisms, idiosyncratic semantic associations and word approximation [223-225] and negative language symptoms such a poverty of speech and simplification of grammar [226-228]. Notably, they also comprise difficulties to convey content, illogicality, perseveration, over-inclusion and over-abstraction as well derailment from the intended topic [223]. To a certain degree, this has been linked to a loss of voluntary control over trains of thought, which are directly transferred to spoken language. Linguistically, patients' speech is mainly characterized by unusual lexical access, as exemplified by stilted speech and neologisms, flattened intonation (i.e. aprosody) and pitch as well as distorted pragmatics [223,229-231]. Distorted pragmatics describes the relationship between language and context, which is often disturbed due to patients presuming information that is not actually available or using indirect references to people or objects that are not clear to the listener [232,233]. Together, language impairments add another level of difficulty to social interactions and represent a domain of higher-level cognitive disturbances that is particularly perceivable to the outside world [133].

## **Section II: Pharmacological treatment of cognitive dysfunction**

Over the last two decades, increasing awareness regarding the significance of cognitive dysfunction has prompted a growing number of efforts to identify pharmacological compounds with robust pro-cognitive efficacy.

### *Antipsychotic and antidepressant medication*

The effects of first- (FGA) and second-generation antipsychotics [234] on cognitive dysfunction have been studied extensively [234]. Overall, these studies reported at most a modest effect on cognitive deficits with some evidence for greater

efficacy of SGAs [235,236]. However, data from the “Clinical Antipsychotic Trials of Intervention Effectiveness” (CATIE) study showed no difference between FGA and SGA [237]. Data from first-episode patients also indicates that their cognitive improvements are comparable in magnitude with practice effects observed in healthy controls, which likely have confounded the results of many methodologically less sound studies [238].

Cognitive improvements have also been attributed to reduced psychopathology [239] and generally improving function [240]. Overall, the pro-cognitive effects of FGA and SGA in stable patients appear to be comparable and are not regarded as clinically relevant [241]. Conversely, evidence in antipsychotic-naïve patients indicates that even relatively low doses of a D2-receptor antagonist, risperidone, lead to a measurable worsening of spatial working memory [242]. Moreover, extrapyramidal and metabolic side effects as well as of concurrent anticholinergic medication might also worsen existing cognitive deficits [243,244].

The cognitive effects of antidepressant augmentation of antipsychotics have also been studied repeatedly. In contrast to the beneficial effects of this strategy on negative and depressive symptoms [245], there is no evidence for a clinically meaningful improvement in any cognitive domain [246].

#### *Direct modulation of major neurotransmitter systems*

For the pharmacological treatment of cognitive deficits, scientists have focused on the dopamine (DA), 5HT (serotonin) and Glu (glutamate) neurotransmitter systems and to a lesser extent on NE (norepinephrine) and ACH (acetylcholine). All appear to play a crucial role in the pathogenesis of various clinical and cognitive symptoms [247-249]. Furthermore, they all share one important property, namely a Yerkes Dodson

inverted U-shaped function that regulates their effects on networks involved in cognitive processes. This concept can be easily illustrated by looking at D1 receptors and pyramidal cells in the dorsolateral prefrontal cortex (DLPFC). Optimal, intermediated levels of DA stimulating these receptors reduce neural noise and thus enhance cognitive function. Low levels of D1 receptor stimulation increase NMDA-receptor mediated neural firing - leading to comparably more noise and thus impairing cognitive processes such as working memory. On the other hand, high levels of D1 receptor stimulation largely suppress NMDA receptor mediated neural firing, also impacting cognition negatively [250,251]. This implies an optimum middle range of dopaminergic stimulation while either too little or too much DA impairs the tuning of prefrontal pyramidal neurons and impairs cognition, which has been demonstrated in a variety of species [252].

This notion is also supported by genetic studies on COMT, the major enzyme catabolizing DA in PFC [253] although these have mixed findings. Neuroimaging studies have shown that genetic variants with high COMT activity are positioned to the left, those with lower activity nearer the optimum of the inverted U curve. This position predicts nonlinear response to amphetamine stimulation [254] as well as interactions between dopamine synthesis and prefrontal response [255]. Task-related and task-unrelated prefrontal functions respond in opposite ways to genetic variation in dopamine synthesis, suggesting a tuning mechanism [255]. Additionally, interacting genetic variants in COMT have also been found to affect PFC in an inverted U fashion [256].

Importantly, an inverted U-shaped pattern is also described for noradrenergic neurons originating from the locus coeruleus (LC) [257]. Neural activity in the LC is characterized by tonic and phasic firing that leads to tonic and phasic NE release,

respectively. Tonic firing is stimulus-independent while phasic-firing is stimulus-dependent [258]. Very low tonic firing represents drowsiness and distractibility thus impeding cognitive performance. Very high tonic firing leads to stress that in turn again impedes performance. Therefore, moderate tonic firing facilitates prominent phasic firing [259]. A crucial region impacted by NE is the PFC. Here, again both deficient as well as excessive NE-mediated signaling leads to deficits in working memory [260-262]. An optimal firing mode is needed for an advantageous function of the fronto-parietal network which is involved in attention and working-memory processes [249].

Similarly, for the  $\alpha$ -7-nAChR within the DLPFC benefits are evident in lower doses and decrease in higher doses which was observed using the agonist PHA543613 [263]. In rhesus macaques, Castner et al. observed improvements in working memory performance using the compound AZD0328 that also targets  $\alpha$ -7-nAChR. However, they also observed worsening when administering both high as well as ultra-low-doses [264].

Serotonergic neurons are distributed across the brain with a high density in the PFC [265] and hippocampus [266-268]. Serotonin has also been implicated in the pathophysiology of cognitive impairments – such as attention, working memory and learning in schizophrenia [268-270]. This assumption is based on observations presented by Cano-Colino et al. who studied the impact of 5HT on spatial working memory and delineated compromised functioning at both very high and very low concentrations [271]. Tryptophan – the precursor amino acid of 5HT – also shows an inverted U-shape relationship to cognition [272].

These findings highlight the complex neurobiological mechanisms governing monoaminergic modulation of cortical circuits and cognition, which represent a major challenge for pharmacological research. This might also explain why so far, strategies



focusing on direct receptor modulation have not yielded any consistent positive results. In fact, a recent meta-analysis on pharmacological cognitive enhancers in schizophrenia did not detect any discernable benefit for *any* type of medication over placebo [273].

#### *Allosteric modulators*

As a result of the negative findings in these trials, indirect approaches, (specifically, allosteric modulators) have recently been gaining increasing attention (Table 1). Traditionally, most drugs act as a direct ligand when coupling to receptors, thus either inhibiting or activating the receptor. However, specificity is compromised as most receptors have a variety of subtypes characterized by different functions. Therefore, a direct ligand tends to be less selective and more likely to cause side effects.

**Table 1: Pharmacological approaches.**Pharmacological treatments of cognitive impairment associated with schizophrenia using an allosteric modulator, neuroplastic or anti-inflammatory approach.

Neurotransmitter system	Target	Compound and Mechanism of action	Results	Reference
FGA and SGA	Preferentially D2 receptors	e.g. haloperidol; risperidone  Antagonism	Modest effect on cognitive deficits: SGA > FGA	[1,2]
			No difference between FGA and SGA	[3,4]
			Possible worsening of working memory	[3-5]
Glutamatergic system	NMDA receptors	Glycine; serine; d-cycloserine; bitopertin	Promising results	[6-15]
		PAMs targeting the GluN1-subunit	Negative results	[16-18]
		sGC stimulator	Promising preclinical results	[19]
	AMPA receptors	PAMs	Promising results	[20-23]

			Overweighing side effects	[24-26]
	Kainate receptors	PAMs	Studies are scarce	[27]
	mGluR	e.g. pomaglumetad; MPEP  PAMs	Studies are scarce	[28]
			Overweighing side effects	[29]
			Promising results	[30,31]
GABAergic system	GABA-A receptor	TPA023 (targeting alpha-2 and -3-subunit)	Inconsistent results	[32-34]
		PAMs		
		Compounds targeting alpha-5-subunit	Overweighing side effects	[35]
		NAMs		
	GABA-B receptor	Agonists/antagonists; (negative) allosteric modulators	Limited to animal models	[35-38]

Dopaminergic system	D1 receptors	Agonists	Worsening psychotic symptoms	[39]
		DETQ; ASP4345	Promising results	[40,41]
		PAMs		
Cholinergic system	Muscarinic receptors	PAMs	Still in pre-clinical phase	[42-45].
	Nicotinic receptors	Partial agonists	Positive effects solely in non-smokers due to desensitization	[46-49]
		e.g. Galantamine; compounds targeting $\alpha 7$ -nAChR	Inconsistent results → further studies required	[50,51]
		PAMs		
Serotonergic system	e.g. 5HT <sub>6</sub> receptors	Antagonists; Agonists	Inconsistent results → further studies required	[52,53]

		PAMs; NAMs	Further studies required	[54]
EPO	EPO receptors	Pleiotropic effects	Promising transdiagnostic results	[55-64,65,66,67]
			Specific monitoring advisable	[68-75]
Anti-inflammatory approaches		e.g. minocycline; simvastatin; omega-3-unsaturated fatty acids; N-acetylcystein; COX-2-inhibitor	Promising results	[76-86]
			Inconsistent result → further studies required	[87-93]

Furthermore, pharmacological compounds which directly block or stimulate certain receptor types have one crucial disadvantage. They follow a “homeostasis” approach by imposing fixed, inflexible values on synaptic parameters. However, this likely impedes the brain’s ability to quickly adapt its synapses and neural circuits in respond to cognitive demands using its stored knowledge to predict appropriate values [274]. This predictive regulation strategy is known as “allostasis”. In contrast to homeostatic regulation of synaptic function, which can achieve stability only after an abnormal parameter was detected, allostatic regulation utilizes parameter alteration to maintain stability [275,276].

Antipsychotic drugs, accordingly, follow a “homeostasis” strategy by blocking dopamine receptors, and target not only D2- but also D3- and D4-receptors implicated in a variety of functions including cognitive processes [277]. Hence, antagonizing D2-like receptors using antipsychotics counteracts positive symptoms but can also induce deterioration of cognition in a dose-dependent manner [242,244,278-283].

In contrast to such direct receptor agonists or antagonists, allosteric modulators bind to remote parts of the receptor’s active site and require the endogenous ligand to improve receptor function, thus preserving the brain’s inherent ability for allostatic regulation to a much greater degree. Therefore, positive allosteric modulators (PAM) might be particularly useful for ameliorating network dysfunctions underlying a particular cognitive impairment. Additionally, they might be advantageous when aiming to obviate receptor-desensitization and -downregulation [284]. For example, smoking leads to desensitization of nicotinic acetylcholine receptors due to chronic nicotine exposure, thus impeding the use of nicotinic agonist to improve working memory and attention disturbances in patients who smoke [285,286]. Another potentially useful feature of allosteric modulators is the so-called ceiling effect. This is characterized by

a plateau regarding a drug's neurobiological effect leading to a wider therapeutic margin [287] and, consequently, better safety profile.

One generally distinguishes between allosteric modulators amplifying (positive allosteric modulators, PAM) and allosteric modulators suppressing receptor activity [287-289]. A third group is termed as "silent allosteric modulators" (SAM) [290]. These modulators are also called neutral allosteric ligands since they do not possess any impact on the receptor's activity. Instead, they compete with and potentially antagonize negative allosteric modulators (NAM) and PAMs. However, SAMs currently do not play any role treatment approaches [291]. Rather, they can help elucidate the receptor binding profile of NAMs and PAMs.

Allosteric modulators can also possess intrinsic activity at higher doses [292-294]. Naturally, this principle can be extended to other important targets such as metabotropic glutamate (mGluR), nicotinic, muscarinic as well as dopaminergic receptors [295-299].

### Glutamatergic system

Interestingly, the mechanism of allosteric modulation is extensively exploited in the brain, underscoring its potential. This is especially true for the glutamatergic system. Importantly, there is converging evidence for a role of disturbances in glutamatergic neurotransmission – especially NMDA receptor hypofunction – for both the clinical and cognitive symptoms of schizophrenia [300-303]. NMDA receptor hypofunction in particular has been implicated as a cause for E/I imbalance abnormal gamma oscillations in schizophrenia [304].

Overall, glutamatergic abnormalities involve both mGluR and ionotropic glutamate receptors [299,305,306]. While the mGluR-family is characterized by its

modulatory function, the ionotropic glutamate receptor exhibits fast excitatory properties [306]. Ionotropic glutamate receptors comprise three groups, namely NMDA- [307], AMPA- [308] and kainate receptors [309]. While NMDA receptors remain the primary focus of the glutamatergic hypotheses of schizophrenia, more recently AMPA- and to a lesser extent also kainate receptors have also been studied [309,310]. There is converging evidence from studies with the ketamine and phencyclidine, which target the NMDA receptor, in both humans and animal models that a disruption of NMDA receptors leads to wide ranging cognitive deficits [300,303]. These include impairments in perception [119], cognitive flexibility [311], attention [312], working memory [313] and learning [314].

NMDA receptors always contain two GluN1-subunits binding glycine that are then combined with either two GluN2-subunits or one GluN2-subunit and a GluN3-subunit[307]. Since direct NMDA receptor agonism can induce excitotoxicity due to glutamatergic overload [305], researchers recently focused on alternative mechanisms. The search for novel PAMs binding to NMDA receptors focuses on GluN1- and GluN2-subtypes, as these are the most prevalent ones [299,315]. Findings from NAMs (traxoprodil and BMT-108908) targeting GluR2B support the effects of glutamatergic PAMs binding to this receptor subtype and its involvement in cognitive processes such as recognition memory and learning as shown in non-human primates [316]. Nevertheless, research regarding novel allosteric modulators targeting the NMDA receptor is still in its early phase [315,317,318]. Glycine, which is crucial for NMDA receptor mediated glutamatergic neurotransmission, is a prominent example for an endogenous allosteric modulator [319]. The activation of NMDA receptors not only requires Glu binding to the GluN2-subunit, but also glycine binding to the GluN1-subunit [320,321]. In contrast to the GluN1-subtype, the GluN2-subunit is



characterized by 4 isoforms with differing distribution in the CNS [322]. Due to evidence for alterations in glycine-mediated processes in neuropsychiatric disorders, namely schizophrenia and ASD, glycine has been implicated for therapeutic approaches targeting cognitive dysfunction [323,324].

D-Serine, another endogenous co-agonist is as potent as glycine, and binds to the glycine site of the NMDA receptor as well. In addition, glycine modulates d-serine metabolism by inhibiting serine racemase [325]. Several studies using d-serine, d-cycloserine and glycine examined effects of these substrate on cognitive impairments in patients, but with overall negative results [326]. Administration of d-cycloserine might lead to amelioration of cognitive deficits when co-administered with antipsychotics other than clozapine [327-329]. However, it appears to be associated with an inverted U-shape response curve and its positive effects could not be maintained during long-term treatment [330,331].

Re-uptake inhibition of glycine is another potentially relevant mechanism, exemplified by sarcosine and bitopertin. Yet, a recent meta-analysis failed to show consistent pro-cognitive benefits for both compounds [332,333]. Inhibiting DAAO, the enzyme catabolizing [334,335] glycine, might also improve cognitive functioning [336-338]. Sodium benzoate is a DAAO-inhibitor that showed promising initial results in treating cognitive impairments in patients with schizophrenia when used as an add-on therapy [334,335], yet data await further replication. Recently, a double-blind, randomized, placebo-controlled phase 2 trial with BI425809 as a glycine transporter-1 inhibitor reported first encouraging findings in patients with schizophrenia [339]. Targeting mechanisms downstream of the NMDA receptor might also be a promising avenue. Glutamate binding to NMDA leads to calcium influx that in turn activates nitric oxide synthase to produce NO, which in turn stimulates soluble guanylyl cyclase (sGC)

to form cyclic GMP [340]. Accordingly, evaluation of an sGC stimulator as a potential treatment for cognitive impairment in schizophrenia is underway.

One important goal of NMDA receptor modulation is to promote long-term potentiation (LTP) and memory performance [341], and to increase the release of neurotrophic factors [341,342]. To this end, AMPA receptors are another promising target for allosteric modulation strategies [310,343,344]. AMPA receptors modulate NMDA-R-activity and show altered density in patients with schizophrenia – in particular, increased density in the PFC and diminished density in the hippocampus. Pro-cognitive effects were indeed observed in preclinical and small-scale clinical studies [345,346]. Overstimulation however leads to detrimental effects, namely seizures and apoptosis [347-349].

Kainate receptors have less frequently been the focus of research compared to NMDA and AMPA receptors [310]. However, to our knowledge studies regarding allosteric modulation of kainate receptors are still scarce [350]. In sum, the pro-cognitive effects of PAMs targeting ionotropic glutamatergic receptors are at best inconsistent, as shown by a recent meta-analysis [351].

Regarding metabotropic glutamate receptors, one distinguishes eight subtypes. These are classified into three broad groups with differential involvement in cognitive processes [352], making them promising targets [353]. Group I receptors mGluR1 and mGluR5 are involved in LTP and long-term depression (LTD), mechanisms crucial for neural plasticity [354,355], while group II receptors mGluR2 and mGluR3 show neuroprotective effects – in particular protection against NDMA-mediated excitotoxicity [356]. Group III receptors include mGluR4, mGluR5, mGluR6, and mGluR8 [297]. Recent observations in patients with schizophrenia treated with pomaglumetad, a highly selective mGluR2 and mGluR3 agonist, indicated that only specific patient

groups might benefit from treatment with mGluR-2-PAMs, as only patients in the early phase of the disorder showed improvements in global psychopathology [357]. However, the effects of pomaglumedad on cognitive deficits remains to be investigated. An mGluR5-PAM might facilitate the improvement of cognitive deficits due to its interaction with NMDA-R [358]. However, this approach appears to be associated with considerable side effects in the form of seizures, particularly in mGluR5-PAMs with intrinsic activity. It has therefore been suggested that beneficial modulation of LTP and LTD would have to rely on mGluR5-PAMs without intrinsic activity [359].

Preclinical reports for positive allosteric mGluR3 modulators indicate potential neuroprotective properties [360,361]. Studies using NAMs offer indirect support for a benefit of mGluR5 PAMs. For instance, the NAM MPEP intensified cognitive impairments in rats previously treated with phencyclidine [362].

### GABAergic system

GABAergic neurons play a crucial role in the disruption of neural circuits in bipolar disorder and schizophrenia [53,363,364]. Furthermore, they are closely involved in schizophrenia-associated cognitive deficits [365,366]. A recent study observed decreased GABA-levels in patients with first-episode psychosis, which was correlated with illness severity and deficits in visual learning, working memory, attention, speed of processing and reasoning [367]. As outlined above, this is primarily attributable to reduced inhibition of excitatory pyramidal cells by PV neurons contributes, which results in widespread E/I imbalance in cortical microcircuits [52].

For GABA-A receptors, the subunits alpha-2, -3 and -5 are of particular relevance for cognitive processes. While benzodiazepines are PAMs binding to GABA-A receptors, they lack subunit selectivity [368] and appear to further impair cognitive

function [369,370] underscoring the need for highly selective allosteric modulators. Importantly, depending on the specific subunit, pro-cognitive effects might be attained either by a PAM [371,372] or NAM [371,373]. However, clinical trials with patients with schizophrenia receiving the PAM TPA023, targeting the  $\alpha$ -2 and -3-subunit, revealed inconsistent results regarding amelioration of cognitive dysfunction [372,374]. NAMs of the  $\alpha$ -5-subunit are still evaluated in pre-clinical studies with respect to the improvement of working memory, but appear to have side effects such as seizures, anxiety or even a worsening of psychotic symptoms [375]. Quercetin – a NAM targeting GABA-A receptors – reduces MK801-induced locomotor hyperactivity *in vivo* by disinhibiting glutamatergic transmission elicited by GABAergic hyperactivity in the PFC. Locomotor hyperactivity in rodents model positive symptoms. Notwithstanding aiming to treat psychosis, this compound corroborates the potential benefits of allosteric modulators binding to GABA-A receptors [376,377]. Other selective compounds did not prove to be successful due to side effects [368].

GABA-B receptors are metabotropic receptors that are particularly relevant for neurodevelopment by promoting neurotrophic processes [378] and neural plasticity [379] especially LTP [380]. Notably, they have also been implicated in cognitive dysfunction in schizophrenia [381,382] including working memory [383,384]. However, data about allosteric modulators targeting GABA-B receptors scarce and remain limited to animal models [375,385-387].

### Dopaminergic system

Since antipsychotics can partly worsen cognitive function by inhibiting DA receptors in ventral striatal and cortical areas, it is of particular importance to develop

alternative approaches [388,389]. Dopamine D1-like receptors, comprising D1 and D5-receptors, have been suggested as targets to ameliorate cognitive deficits in patients with schizophrenia [390,391]. Attempts to target D1-like receptors by agonists, DA transporter inhibition, or MAO- and COMT inhibition were however not successful due to worsening of psychotic symptoms [295]. So far, most studies with dopaminergic PAMs are in-vitro studies. For instance, in transgenic mice over-expressing D1 receptors, the D1-receptor PAM DETQ led to improved performance in an object recognition task and in cortical ACH release [392]. A phase 1 clinical trial with the D1-receptor PAM ASP4345 showed improvements in psychomotor function, visual attention and corresponding improvements in neurophysiological markers [393]. However, studies in humans are still lacking.

### Cholinergic system

As mentioned before, both nicotinic as well as muscarinic-(M)-cholinergic receptors play an important role in the pathophysiology of cognitive deficits in schizophrenia. Associations between muscarinic receptors and cognition are supported by studies using xanomeline, a M1/M4 receptor orthosteric agonist that led to cognitive improvements in patients with schizophrenia [394]. Both the M1 and M4 receptors are of particular relevance [395]. Here, M1 receptors are involved in memory and attention processes and the M4 receptors appear to be crucial for anti-psychotic treatment. Unfortunately, the development of muscarinic agonists initially failed due to peripheral – especially gastrointestinal – side effects. However, combining xanomeline with tropium (which blocks peripheral acetylcholine receptors) showed significant improvement of schizophrenia symptoms measured with the “Positive and Negative Syndrome Scale” (PANSS) but a much better safety profile [396]. Unfortunately,

cognitive measures were not reported. Attempts to selectively target the muscarinic receptor subtypes are complicated by the considerable similarities of each subtype. Therefore, PAMs which promote the affinity of ACH to the muscarinic receptor's orthosteric binding site have increasingly been investigated [397-399]. However, these compounds are still in the pre-clinical phase [395,400-402].

Additionally, the nicotinic system has been a major focus. An estimated 70% of patients consume nicotine, and a self-medication strategy for the cognitive and clinical symptoms of the disorder is generally assumed to be the cause [403,404]. Specifically, an association between the nicotinic system through altered  $\alpha 7$ -nAChR with cognitive impairment is supported by genetic studies [405]. So far, a number of compounds selectively targeting  $\alpha 7$ -nAChR have been developed, which either did not improve or even worsened working memory and other cognitive processes in patients with schizophrenia that were smokers. Positive effects were observed solely in non-smokers. Suboptimal results using partial agonists have been primarily attributed to a desensitization of nAChR in smokers [286,406-408].

Some scientists tried to discover PAMs targeting nicotinic receptors – especially since PAMs do not tend to lead to desensitization. Galantamine is a well-known PAM that is used in Alzheimer's disease – however without significant results. A pilot study investigating the effects of galantamine and nicotine in healthy populations [409] indicated that positive allosteric modulation in nAChR is feasible, but that further research is required to establish an optimal dosing range. Unfortunately, phase 3 trials evaluating the effects of compound binding  $\alpha 7$ -nAChR failed to show a beneficial effect on cognition [298]. With respect to galantamine, results were not statistically significant regarding the primary outcomes on negative symptoms measured with the PANSS and cognitive symptoms measured with the MCCB. Yet, global function and

verbal recall improved significantly in patients with schizophrenia after they received galantamine in combination with citicoline. Citicoline was administered to counteract a possible desensitization of the nAChR [410].

### Serotonergic system

Involvement of the 5HT system in cognitive dysfunction, in particular in the perturbation of short- and long-term memory as well as learning [411,412] has been observed in schizophrenia [413]. Several trials with 5HT6-antagonists have been conducted. These comprised animal studies as well as clinical trials with patients with Alzheimer's disease and schizophrenia targeting long-term memory with some initially promising results [414]. However, direct early studies with serotonergic agonists and antagonists failed to improve cognitive impairments, most likely due to a lack of subtype specificity [415]. Despite the potential of allosteric serotonergic modulators, so far there is still a relatively limited number of pre-clinical studies examining PAMs and NAMs in the context of cognitive impairments [416].

Overall, the development of allosteric modulators that target the major neurotransmitter systems appears to be a promising approach. However, presently more studies in healthy subjects and patients with schizophrenia are urgently needed to corroborate preclinical findings. While research efforts related to less prominent neurotransmitter systems beyond the scope of this review are also ongoing, so far these have similarly yielded no clinically relevant positive findings.

### *Erythropoietin*

Another line of research has focused on the study of neuroprotective compounds, especially erythropoietin (EPO). EPO is a glycoprotein and growth-factor synthesized in and secreted especially by the fetal liver and adult kidney. Moreover, approximately 15-20 % is synthesized and secreted in other parts of the body including cerebral endothelial cells, astrocytes, hippocampus and the cerebral cortex [417-419].

EPO does not only regulate erythropoiesis but is also characterized by pleiotropic effects in the CNS mediated by a brain specific EPO receptor [419]. These comprise the reduction of glutamate-based neurotoxicity [420], enhancement of dopamine- and acetylcholine-release, the reduction of apoptosis as well as the inhibition of microglial function and pro-inflammatory cytokines such as IL6 and TNF- $\alpha$ 1 [421,422].

In addition to further positive effects on the integrity of the blood-brain barrier (BBB) and on oxidative stress, EPO also shows modulatory effects on neurogenesis by promoting neuronal proliferation and differentiation [423,424]. This is particularly relevant as cognitive impairment in schizophrenia has also been linked to disturbed adult neurogenesis [425]. EPO synthesis and secretion are induced by hypoxia and ischemia [426]. The binding of EPO to its specific homodimerized receptor causes a downstream cascade activating further transcription factors, kinases, and also increases calcium. The mechanisms appear to facilitate cell differentiation and neural plasticity [423,427,428].

EPO is most commonly used to treat anemia in patients suffering from chronic kidney failure. However, over the past decades several studies have demonstrated positive effects in the brain. These include the reduction of BBB leakage [429,430], inflammation [431,432] and the amelioration of cognitive deficits in neuropsychiatric disorders [424,433-437].

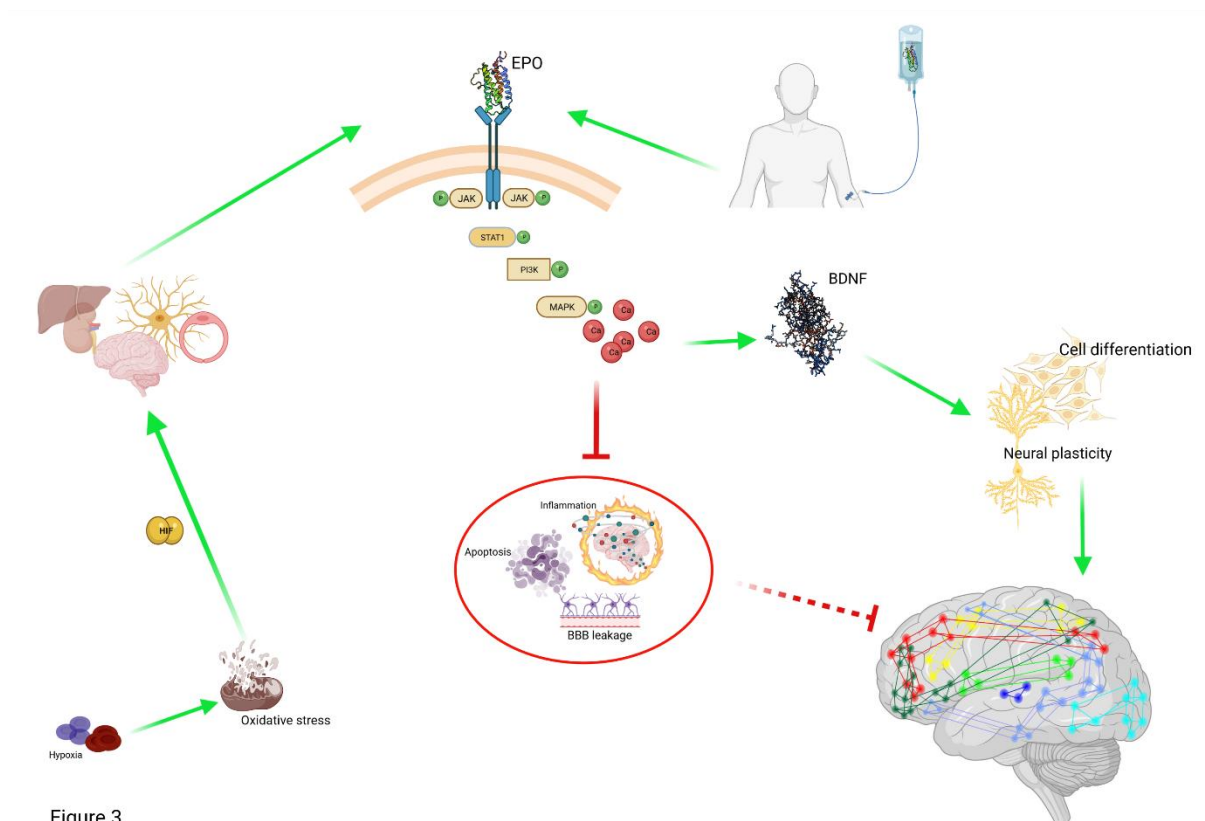


Most importantly, consistent pro-cognitive effects were reported for schizophrenia [424,434]. These effects were accompanied by a reduced decline of gray matter volume in a network of brain regions closely involved in attention and memory processes [438]. Interestingly, improvements of cognitive deficits were also observed in bipolar disorder [437], chronic-progressive multiple sclerosis [433] and Parkinson's disease [439] clearly indicating EPO's transdiagnostic relevance.

In contrast to previous assumptions, current evidence strongly supports a direct effect of EPO on brain function and thus on cognition by enhancing neurotrophic and neuroprotective processes [434,435]. For instance, EPO appears to induce the production of brain-derived neurotrophic factor (BDNF) in the hippocampal tissue. In addition, in patients with schizophrenia, a decrease of S100 protein – a marker for glial damage – predicted a better clinical outcome after one month of treatment [434,438,440,441]. Studies with mice receiving EPO showed an increase of LTP in the hippocampus. Additionally, antidepressant effects in treatment resistant patients with major depression have been reported [437,442]. A longitudinal fMRI study reported an increase of hippocampal activation in healthy subjects seven days after infusion of EPO with corresponding improvements in verbal fluency and working memory. These effects were evident without any obvious hematopoietic effects [435] (Figure 3).

Several aspects of the effects of EPO remain to be elucidated. This includes the optimal duration of EPO treatment and the durability of its pro-cognitive effects. Importantly, EPO might promote the progression of some forms of tumors expressing EPO receptors as a result of its anti-apoptotic effects and its impact on angiogenesis [443,444]. This appears to apply to some forms of breast cancer [445,446] as well as head and neck cancer [447]. Sufficient pretreatment screening is therefore crucial. Regular safety monitoring is also required to manage the potential risk for thrombosis

[448] and hypertension [449]. The likelihood of the former can already be mitigated by reducing iron intake, considerably limiting the hematopoietic side effects of EPO [450]. Furthermore, these might also be surmountable by a modification at the molecular level – i.e. carbamylation of EPO [451,452]. This strategy takes advantage of differences between the brain-specific and hematopoietic EPO receptors [452-454].



**Figure 3: Pro-cognitive effects of erythropoietin**

Synthesis of erythropoietin (EPO) is induced by hypoxia and shows pleiotropic effects that go far beyond its hematopoietic effects. In the brain, EPO shows anti-inflammatory and anti-apoptotic effects and reduces BBB leakage. Beyond these neuroprotective effects, EPO also induces differentiation neural progenitor cells, increases dendritic spine density. Together these effects are the basis for the pro-cognitive properties of EPO.

Interestingly, the beneficial effects of EPO on cognition might also extend to cognitive deficits induced by electroconvulsive therapy (ECT). Furthermore, evidence from animal studies suggests that ECT might also act partly through the intracerebral induction of EPO [455]. ECT is an effective treatment for patients with schizophrenia with an insufficient response to clozapine [456]. Cognitive side effects following ECT are transient and appear to be less common in patients with schizophrenia than in patients with major depressive disorder (MDD) [457,458]. Yet, they can still be a limiting factor due to an increased likelihood of patients refusing to continue treatment. Several studies indicate an improvement in some cognitive domains over time after receiving ECT [456], which would be compatible with the purported influence of ECT on intracerebral EPO. Based on recent findings in animal studies, it has even been suggested [459] that EPO and ECT should be combined to counteract these transient cognitive deficits. Efforts to examine the effects of such a combination in patients with uni- or bipolar depression are currently underway [460], which could pave the way for similar studies in patients with schizophrenia.

#### *Anti-inflammatory approaches*

There is increasing evidence that a chronic low level inflammatory syndrome might contribute to the pathophysiology of schizophrenia [461-464]. A variety of peripheral pro-inflammatory markers have been shown to be increased in subgroups of patients with schizophrenia [465,466]. Moreover, meta-analytic evidence indicate a correlation between inflammation and cognitive dysfunction in patients with schizophrenia [467]. It has been hypothesized that chronic inflammation might lead to

a disruption of the BBB in these patients, which could facilitate intracerebral inflammatory processes [468-471]

Minocycline is a second-generation tetracycline which also inhibits microglial function and appears to ameliorate cognitive and negative symptoms in patients with schizophrenia when co-administered in early phases of the disorder [472]. Several studies indicate an interaction between minocycline and microglia [473], pro-inflammatory cytokines [474] and free radicals [475,476]. As a result minocycline has been associated with both anti-inflammatory and anti-apoptotic properties [477].

Simvastatin is used to treat hyperlipidemia and has additionally demonstrated pleiotropic effects including the decrease of pro-inflammatory cytokines and the amelioration of both cognitive and positive symptoms in patients with schizophrenia [478-481]. Celecoxib, a cyclo-oxygenase-2-(COX-2)-inhibitor has also been shown to improve cognition in patients with schizophrenia [482].

Furthermore, omega-3-unsaturated fatty acids, which are regarded as anti-oxidants have been evaluated. When combined with ascorbic acid and  $\alpha$ -tocopherol they appear to improve global psychopathology [483], but overall results have been mixed [484-487]. The number of studies examining the impact of unsaturated fatty acids on schizophrenia-associated cognitive impairment is limited and equally inconsistent [485,488-490] with some indication for a positive effect on semantic memory and language [491].

N-acetylcystein reduces redox dysregulation and oxidative stress through its effects on glutathione activity and improves mitochondrial integrity [492,493]. As a result, it has anti-inflammatory properties and appears to normalize glutamatergic and GABAergic neurotransmission to some degree [487,493]. So far, studies have reported improvements in negative symptoms [494,495] and working memory [496]. Overall,

while the exact pathophysiological mechanisms underlying the link between inflammation and cognitive impairments in schizophrenia remain to be elucidated, these findings highlight the potential therapeutic relevance of anti-inflammatory approaches, particularly in the early stages of the disorder [472,497]. Yet, current evidence regarding the utility of the aforementioned anti-inflammatory and neurotrophic agents for improving cognitive dysfunction is still regarded as inconclusive, emphasizing the need for larger, well-controlled studies [498].

### **Section III: Non-pharmacological strategies**

#### *Cognitive remediation therapy*

For several decades, cognitive remediation therapy (CRT) has been utilized to improve cognitive performance and ultimately daily functioning in schizophrenia. CRT exploits the inherent neuroplastic properties of neural circuits, which are essential for their development, refinement and reorganization, in response to the targeted training of cognitive processes [499]. Originally, CRT programs for schizophrenia were closely modeled after the neuropsychological concepts used for patients with traumatic brain injury [500] but have evolved considerably based on more current concepts of the specific underpinnings of cognitive dysfunction in schizophrenia [501-503]. Overall, the benefits of cognitive remediation include moderate improvements of cognitive performance across all relevant domains and more importantly psychosocial functioning, but also a reduction of clinical symptoms [107,504]. The concurrent improvement in daily functioning after cognitive remediation has been repeatedly confirmed in meta-analyses [504,505]. The integration of cognitive remediation with psychiatric rehabilitation programs is associated with particularly beneficial outcomes because it closely links the acquisition of cognitive skills to real-life situations [506,507]. Thus, its potential proximity to real world situations is on one of the inherent advantages of cognitive remediation. This also limits the usefulness of predominantly computer-based programs, which might negate this advantage. In this context, one central principle involves intensive support from a therapist to modify behavioral strategies in order to improve cognition and tie that to everyday behavioral exercises [508].

A complementary approach involves the development of compensatory strategies in order to modify the interaction of patients' cognitive strengths and

weaknesses with the environment [500]. Cognitive remediation affects all relevant cognitive domains and appears to facilitate brain reorganization on both the micro- and macro-circuit level [509]. However, our current understanding of the neurophysiological consequences of cognitive remediation remains limited due to the considerable heterogeneity of available neuroimaging studies.

Several meta-analyses have tried to identify predictors factors for a positive response to CRT, but with relatively inconsistent results. One recent study reported a positive association of premorbid IQ, baseline cognition and training task progress, i.e. improvement on CRT tasks [510]. Interestingly, there is conflicting evidence regarding the differential utility of cognitive remediation in early versus chronic schizophrenia. In a recent meta-analysis, effect sizes for global cognitive improvement were somewhat larger for chronic schizophrenia compared to early schizophrenia [511]. Conversely, other studies have reported that younger, less chronic patients receiving lower doses of antipsychotic medication respond best to these types of intervention [512,513]. Overall, current evidence points to a moderate effectiveness of cognitive remediation across illness stages, making it the most established and most universally recommended approach among pro-cognitive interventions for schizophrenia [514,515].

### *Virtual reality*

The use of virtual reality - interactive immersive computer environments - is an exciting new way to investigate a number of aspects of schizophrenia. This includes the assessment and treatment of cognitive impairments [516]. To a certain degree, virtual reality combines the power and flexibility of computer-based cognitive remediation techniques with the proximity to real-life situations of interactive group

settings. Virtual reality has indeed been used in rehabilitation programs [517]. Patients can practice cognitive tasks and refine compensatory mechanisms in simulated real-life situations. VR-based therapy is well accepted by patients with schizophrenia [518]. Social cognition has been an important focus of virtual reality studies in schizophrenia [519-522], particularly the evaluation and interpretation of social cues from others. Several studies have demonstrated improvements of social cognition in patients after VR-based trainings [521,523,524]. Due to its potential, future studies should expand the use of VR-based cognitive remediation to other domains.

As neural plasticity is use-dependent, it may be a promising strategy to couple pharmacological intervention with CRT/VR-CRT. While questions such as optimal sequence and timing remain to be clarified, such combination may even be required to unleash the full potential of pharmacological approaches. However, we are not aware of any respective study.

### *Aerobic physical exercise*

There is growing interest in exercise interventions, especially aerobic training, as an add-on treatment for patients with schizophrenia. In addition to positive effects of exercise on positive and negative symptom severity, need of care, social and global functioning, and quality of life [525-530] aerobic physical exercise appears to confer a number of neurocognitive benefits. Meta-analytic evidence indicates a general performance increase in a pooled assessment of cognitive functions following exercise interventions [531]. However, effects on individual MATRICS domains [532] are rather heterogeneous. Physical exercise appears to be particularly beneficial for working memory, attention/vigilance and social cognition, with effect sizes comparable to cognitive remediation therapy [531,533]. Conversely, there is no consistent evidence



for effects on processing speed, verbal and visual learning and memory, and reasoning and problem solving [531]. Longitudinal studies indicate that exercise-induced improvements may not be sustainable to the same degree across cognitive domains [528,534]. It must be noted, however that existing studies show a large degree of heterogeneity with respect to sample sizes and implemented interventions, differing in duration, intensity, type of exercise and combinations with other interventions [527,535]. The strongest impact on cognition is likely induced by aerobic training and by interventions that are supervised by professional physical activity instructors [531]. The intensity, length, frequency and fidelity required for exercise-based interventions to improve cognition is still unclear. Yet, both exercise dose and the length of interventions have been positively linked to greater cognitive improvements [536,537]. At least 90 min per week of moderate-to-vigorous exercise with blood lactate concentrations of approx. 2.0 mmol/l and intensity levels between 10-13 on the Borg-scale of perceived exertion [538] have been proposed to be required to induce changes in physical fitness, neurocognition and functional outcome [527,535]. This is especially relevant considering that patients' adherence to (group) exercise interventions may be limited by factors such as somatic comorbidities, social anxiety, and sedative effects of antipsychotic medication [526,539]. On the neurobiological level, multiple lines of evidence indicate a central role of exercise-induced multi-level neuroplasticity, which directly counteract some of the pathophysiological processes implicated in schizophrenia [540].

Potential levels of actions include increased gray matter volume [541], white matter integrity [542,543], improved angio- and [544,545] neurogenesis [545-547], epigenetic adaptations [548,549], increased levels of a number of neurotrophic factors [550-552], enhanced dopaminergic, cholinergic and norepinephrinergic

neurotransmission [553-556], normalization of the hypothalamus-pituitary-axis [557] and an improved antioxidant defense [540,558]. Importantly, these proposed mechanisms are predominantly based on animal studies and observations in healthy individuals [540]. In schizophrenia, neuroplastic responses to exercise appear to be attenuated [559] and are further affected by individual risk factors such as polygenic risk [560]. Increased hippocampal volume and concurrent enhancements of verbal short-term memory following three months of endurance training in patients with schizophrenia have been reported [561]. However, this could not be replicated consistently in subsequent studies [542,562,563] and meta-analyses [564]. Nevertheless, other forms of exercise-induced structural and functional neuroplasticity [234,542,543,563,565,566] and increased serum levels of BDNF [550-552] have been reported.

Therefore, irrespective of the remaining uncertainties regarding its exact neurobiological mechanisms, physical exercise remains one of the most promising approaches for the non-pharmacological treatment of cognitive deficits and their psychosocial sequelae in schizophrenia.

### *Brain stimulation*

Non-invasive brain-stimulation (NIBS) techniques in the form of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) constitute an elegant approach for the modulation of neural activity and neuronal plasticity [40,567-571]. Their effects on psychopathology in patients with schizophrenia have been studied extensively. Positive effects on medication-resistant auditory hallucinations have been the most consistent finding [572,573]. However, there is increasing evidence for their efficacy in treating cognitive symptoms in

psychiatric disorders. Improvements in working memory and long-term memory following high-frequency stimulation with rTMS [574,575] have been demonstrated consistently in schizophrenia.

For tDCS, so far positive effects on working memory, attention and social cognition have been reported [574,576]. Interestingly, tDCS applied during the performance of a working memory task lead to greater cognitive improvements than tDCS applied during rest in healthy subjects [577] suggesting a potential benefit for the concurrent use of brain stimulation and cognitive remediation techniques. This observation also implies that tDCS might enhance neural plasticity.

Overall, both NIBS-methods show considerable potential for treating cognitive impairments, but this line of research still appears to be in its early stages and the neurophysiological underpinnings and the rationale for specific stimulation protocols need to be established much more clearly.

## **Section IV: Outlook**

### *The need for a personalized approach*

As reviewed, currently available cognitive enhancement interventions show at best a moderate effect size. On the one hand, this can be attributed to the lack of knowledge about more effective pro-cognitive mechanisms. On the other hand, another important aspect is the great variability of response to pro-cognitive interventions.

Several important factors underlying this phenomenon have been proposed, particularly genetics [578] and patients' baseline level of cognitive functioning. Individuals with low cognitive performance typically respond more strongly to cognitive enhancement interventions. Furthermore, genotypes influencing specific

neurotransmitter or signaling pathways targeted by a compound might have a pronounced effect on the degree of cognitive enhancement [578]. Additionally, the complex neurobiological and neurophysiological mechanisms giving rise to cognitive functions and their disturbance make it highly unlikely that a single approach will be successful for a substantial number of patients. Thus, although large-scale randomized controlled trials offer protection from false positive findings, they also have the potential to disregard the crucial fact that only specific subgroups might benefit from a particular intervention. These issues underscore the need for a personalized medicine approach [113,579,580] and the development of suitable biomarkers based primarily on genetic, neurophysiological and cognitive data.

In general terms, biomarkers are defined as biological parameters of “defined characteristic”, which are utilized as reliable indicators for physiological and pathological processes and for monitoring the “response to an exposure and intervention” [581]. Thus, biomarkers can be used to estimate illness risk and prognosis, to study pharmacodynamics, to evaluate treatment responses, and to predict the effect of a therapeutic intervention [582-584].

### *Cognitive imaging biomarkers*

Functional neuroimaging methods including EEG [585,586], MEG [585] or fMRI have been essential for increasing our understanding of the neurophysiological basis of cognitive impairment in schizophrenia [587,588]. While a more detailed review of these findings is beyond the scope of this article, it is clear going forward that their relevance for this purpose will only continue to increase, not least due to technological advances.

Beyond its traditional role, functional neuroimaging will also be essential for biomarker research [589]. Here, an increasing number of promising biomarker candidates for illness-risk and response to antipsychotic treatment have been reported in recent years [590-593]. Yet, the development of biomarkers suitable for the treatment of impaired cognition is still in its early stages. Ideally, they should closely reflect the targeted neural system [113] pointing to cognitive imaging biomarkers as the most promising candidates [113,578]. Recent studies reporting markers of brain oscillations related to perceptual training underscore the potential of this approach [594,595]. Functional connectomics approaches [596,597] appear to be particularly well suited due to their close links to the dysconnection syndrome [598,599] and the genetic architecture of schizophrenia [600]. The high-dimensional nature of functional neuroimaging data and the imperative to include genetic data of even greater dimensionality strongly argues for the use of machine-learning techniques [590]. In schizophrenia research, functional connectomics have been applied predominantly to resting state data [601], but a cognitive imaging biomarker would have to be based on a cognitive paradigm with sufficient construct validity and sensitivity.

These prerequisites make cognitive imaging biomarkers one of the most challenging classes of biomarkers along with the fact that they require further extensive optimization and validation of cognitive, physiological and technical parameters for multi-site administration. This includes the standardization of task and stimulus parameters, calibration against floor and ceiling effects, the assessment of effect sizes for patient control differences, the assessment of internal and test-retest reliability and the establishment of the relationship between both performance and neural activity measures and clinical and functional measures [113,590].

While cognitive imaging biomarker can be regarded as the gold standard for cognitive enhancement intervention studies, they should be complemented by other biomarker modalities to gain additional mechanistic insights regarding the investigated pro-cognitive interventions. For instance, structural imaging markers including DTI might be used to reveal neuroprotective and neuroplastic effects [40,602-604]. Advances in the imaging of activated microglia using PET [605,606] should allow to monitor the effects of anti-inflammatory treatments in specific brain systems. Blood-based biomarkers and neurotrophic markers such as BDNF [441,607,608] as well as pro- and anti-inflammatory markers [607] have also been evaluated.

#### *Neuroplasticity: a final common pathway*

Many of the therapeutic approaches covered in this review converge mechanistically on the level of neural plasticity. This might not be particularly surprising, given that neural plasticity is crucial for improving cognitive abilities in healthy individuals throughout adult life [609]. On the other hand, the dysconnection syndrome is closely related to fundamental disturbances of neural plasticity and enhancing neural plasticity. Therefore, directly augmenting this essential mechanism for the reorganization of neural circuits and thus reducing the widespread impact of the dysconnection syndrome might currently come closest to a pathophysiology-based treatment of cognitive impairment in schizophrenia is thus probably the most promising therapeutic approach at this moment.

Despite the clear involvement of all the reviewed neurotransmitter systems in neural plasticity and in the etiology of cognitive dysfunction, their pharmacological modulation has so far been less successful than approaches which target neural plasticity more directly and broadly. This is compatible with the notion that abnormal

neural plasticity in schizophrenia is a final common pathway for cognitive dysfunction, also integrating disturbances in individual neurotransmitter systems with inflammatory processes.

Such an interpretation would further imply that intervening at this point of pathophysiological convergence, i.e. at the level of neural plasticity, is practically essential for any successful pro-cognitive intervention. In this context, the mechanistic convergence of widely different treatment options such as cognitive remediation, aerobic exercise, NIBS and EPO highlights the potential for therapeutic synergy [610,611]. This synergy might be further increased by the modulation of neurotransmitter systems with the explicit aim to enhance neural plasticity [612]. Notably, this would also include attempts to restore E/I imbalance in schizophrenia with the goal to normalize attenuated gamma oscillations given increasing evidence for their role in shaping cortical plasticity [613].

In the light of the current state of the field, a development strategy for pharmacological compounds with the aim to synergistically enhance neural plasticity appears to be the most promising. However, one has to acknowledge the enormous challenges associated with such a strategy in terms of study design, required sample sizes and attractiveness for the pharmaceutical industry.

Conversely, for current clinical practice, exploiting existing potentials for therapeutic synergy in treating cognitive dysfunction should already be regarded as essential, but may face its own set of obstacles.

### *Early intervention strategies*

Identifying individuals at heightened risk for psychosis serves as the foundation for intervention studies aimed at avoiding, ameliorating, or delaying progression to

psychosis [614]. This has prompted a surge of research into the prodromal phase of schizophrenia – also termed the “ultra-high-risk state for psychosis” (UHR). Initiating appropriate treatment as early as possible has the potential of improving both the clinical and functional outcome of UHR individuals [615]. Notably, cognitive decline during the prodromal phase is an important predictor not only of functional decline but also of transition to psychosis [616,617]. This emphasizes the specific relevance of improving cognitive dysfunction in UHR individuals. Compared to full-blown schizophrenia, studies of pro-cognitive interventions remain relatively scarce. However, meta-analytical evidence indicates that CRT is effective in UHR individuals [618]. Due to the possibility of preventing further cognitive decline during its early stages, the prodromal phase might constitute a critical period for cognitive enhancement strategies and should be a major focus of research. Yet, the UHR state also warrants particularly great caution when weighing the possible benefits and side effects of treatments, which currently favors non-pharmacological interventions.

### *Transdiagnostic approaches*

A large body of behavioral evidence indicates that cognitive impairments are clearly present across diagnostic categories, albeit to different degrees [578]. For instance, most transdiagnostic studies observed a gradient of cognitive impairment with patients with schizophrenia generally more affected than patients with bipolar disorder [619-625]. In light of these findings and in line with the neurodevelopmental gradient hypothesis, cognitive dysfunction can therefore be regarded as a fundamental feature of neurodevelopmental psychiatric disorders in general [60,626].

Likewise, there is increasing evidence for the existence of distinct biotypes at the systems level across diagnostic boundaries which are characterized by shared



neurobiological features which might not be present in the majority of patients within a diagnostic category [627]. This would imply that studying the relationship between clearly defined transdiagnostic biotypes and cognitive deficits might be a more successful way to develop effective pro-cognitive treatments. In line with the RDoC concept, it might thus be more effective to target the most relevant neural circuitry than to target a specific diagnostic category. This also might substantially increase the potential number of patients, which might benefit from a particular form of therapy. CRT, which in modified form is also effective for patients with MDD, bipolar disorder, ADHD, substance use disorder, ASD, anorexia nervosa, and obsessive-compulsive disorder [628,629] is a primary example of such an approach. However, it should be possible to extend this strategy to other pharmacological and non-pharmacological techniques to enhance neural plasticity as demonstrated the transdiagnostic efficacy of EPO [424,437,438].

### *Conclusion*

The findings and concepts reviewed in this paper clearly implicate the enhancement of neural plasticity as the most promising currently established pathway for improving cognitive deficits in schizophrenia. Furthermore, the recent developments in the field of cognitive dysfunction exemplify the ongoing paradigm shift toward a general conceptualization of many forms of mental illness as information processing disorders with gradual rather than categorical differences in cognitive profiles. Accordingly, ameliorating cognitive dysfunction continues to emerge as an essential goal for psychiatry in general. Addressing the urgent demand for progress in this field depends critically on substantially advancing our knowledge of the neurophysiological and neurobiological basis of intact cognition. Successfully

translating such findings into better pro-cognitive treatments requires an intensified exchange between basic, cognitive and clinical neuroscience on all levels. This should prove to be mutually beneficial as the study of neuropsychiatric disorders itself has increased our understanding of brain function to a considerable degree. Most importantly, these efforts should help to substantially improve patients' long-term outcomes and reduce the considerable burden of schizophrenia.

**ABBREVIATIONS**

5HT	serotonin
ACH	acetylcholine
ADHD	attention deficit hyperactivity disorder
alpha-7-nAChR	alpha-7-nicotinic-acetylcholine-receptor
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASD	autism spectrum disorder
BBB	blood-brain barrier
BDNF	brain derived neurotrophic factor
BMT-108908	NAM selective for the NR2B NMDA subtype
BZD	benzodiazepines
Ca	calcium
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CIAS	cognitive impairment associated with schizophrenia
CNS	central nervous system
CNTRACS	Cognitive Neuroscience Test Reliability and Clinical applications for Schizophrenia
CNTRICS	Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia
COMT	catechol-o-methyltransferase
COX-2	cyclo-oxygenase-2
CRT	cognitive remediation therapy

DA	dopamine
DAAO	d-amino acid oxidase
DETQ	2-(2,6-dichlorophenyl)-1-((1S,3R)-3-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one
DLPFC	dorso-lateral prefrontal cortex
ECT	electroconvulsive therapy
EEG	electroencephalography
E/I	excitatory / inhibitory
EPO	erythropoietin
FGA	first-generation antipsychotic
fMRI	functional magnetic resonance imaging
GABA	gamma-Aminobutyric acid
GAD67	Glutamate decarboxylase 67
Glu	glutamate
HIF	hypoxia inducible factor
ICD-11	International Classification of Diseases 11 <sup>th</sup> Revision
IL6	interleukin 6
IQ	intelligence quotient
JAK	Janus kinase
LC	locus coeruleus
LTD	long-term depression
LTP	long-term potentiation
MAPK	Mitogen-activated protein kinase

MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS cognitive consensus battery
MDD	major depressive disorder
MEG	magnetoencephalography
mGluR	metabotropic glutamate receptor
MPEP	2-methyl-6-(phenylethynyl)-pyridine
nAChR	nicotinic acetylcholine-receptor
NAM	negative allosteric modulators
NE	norepinephrine
NIBS	Non-invasive brain-stimulation
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartate receptor
NO	nitric oxide
OCD	obsessive-compulsive disorder
PAM	positive allosteric modulator
PET	positron emission tomography
PFC	prefrontal cortex
PI3K	phosphoinositide 3-kinase
PV	parvalbumin
RNA	ribonucleic acid
RDoC	research domain criteria
rhEPO	recombinant erythropoietin
rTMS	repetitive transcranial magnetic stimulation

SAD	seasonal affective disorder
SAM	silent allosteric modulator
SGA	second-generation antipsychotic
sGC	soluble guanylyl cyclase
STAT	signal transducers and activators of transcription
SUD	substance use disorders
tDCS	transcranial direct current stimulation
TNF- $\alpha$ 1	tumor necrosis factor $\alpha$ 1
VR	virtual reality

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The authors have declared that there are no conflicts of interest in relation to the subject of this review.





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