Glutamatergic regulation of cognition and

functional brain connectivity: insights from

pharmacological, genetic and translational

schizophrenia research

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The pharmacological modulation of glutamatergic neurotransmission to improve cognitive function has been a focus of intensive research, particularly in relation to the cognitive deficits seen in schizophrenia. Despite this effort, there has been little success in the clinical use of glutamatergic compounds as procognitive drugs. Here, we review a selection of the drugs used to modulate glutamatergic signalling and how they impact on cognitive function in rodents and humans. We highlight how glutamatergic dysfunction, and NMDA receptor hypofunction in particular, is a key mechanismcontributing to the cognitive deficits observed in schizophrenia and outline some of the glutamatergic targets that have been tested as putative procognitive targets for this disorder. Using translational research in this area as a leading exemplar, namely, models of NMDA receptor hypofunction, we discuss how the study of functional brain network connectivity can provide new insight into how the glutamatergic system impacts on cognitive function. Future studies characterizing functional brain network connectivity will increase our understanding of how glutamatergic compounds regulate cognition and could contribute to the future success of glutamatergic drug validation.

Abbreviations

ASST, attentional set-shifting task; 5-CSRTT, 5-choice serial reaction time task; BOLD, blood oxygen level-dependent; CIQ, (3-chlorophenyl) [3,4-dihydro-6,7-dimethoxy-1-[(4-methoxyphenoxy)methyl]-2(1H)-isoquinolinyl]methanone; CPT, continuous performance task; CX516, 6-[(piperidin-1-yl)carbonyl]quinoxaline; DLPFC, dorsolateral prefrontal cortex; EST, patients with established schizophrenia; FC, functional connectivity; FES, first episode schizophrenia; fMRI, functional MRI; HC, healthy control; LC, locus coeruleus; LY2140023, (\_)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6- dicarboxylic acid; mGlu recepor, metabotropic glutamate receptor; MMN, mismatch negativity; NAM, negative allosteric modulation; NOR, novel object recognition; Org 25935, 2-([(1R,2S)-6-methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2- yl]methyl-methylamino)acetic acid; PAM, positive allosteric modulator; PCP, phencyclidine; PFC, prefrontal cortex; Ro 25- 6981, (αR,βS)-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol maleate; RT, response time; SAR218645, (S)-2-(1,1-dimethyl-indan-5-yloxymethyl)-2,3-dihydro-oxazolo[3,2-a]pyrimidin-7-one; SZ, schizophrenia; TUNL, trial-unique, delayed nonmatching to location

The glutamatergic system

Glutamatergic synapses in the CNS, responsible for fast excitatory neurotransmission, play a critical role in a broad range

of cognitive functions. The structure of glutamate synapses and the molecular mechanisms underlying glutamatergic

neurotransmission have previously been reviewed by others in detail (Sanz-Clemente et al., 2013; Sudhof, 2013; Volk

et al., 2015). In mature glutamatergic synapses, a vast array of proteins are involved in the packaging of glutamate into

synaptic vesicles, the localization of these vesicles to presynaptic active zones and the docking and release of the contents of these vesicles into the synaptic cleft (Sudhof, 2013). Postsynaptically, glutamate acts at both ionotropic glutamate

receptors (Glu receptors), including the α-amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid (AMPA), kainate and NMDA receptors, and metabotropic G-protein coupled glutamate (mGlu) receptors to cause depolarisation in the post-synaptic neuron. mGlu receptors are also present on the synaptic bouton that play an important role in the regulation of glutamate release as autoreceptors (see Niswender and Conn, 2010 for review). The synaptic concentration of glutamate is also regulated by glutamate uptake, into both neurons and glial cells,mediated by a range of glutamate transporters (for review, see Vandenberg and Ryan, 2013) and the cystine/glutamate antiporter (System Xc, Bridges et al., 2012). Much research has been dedicated to elucidate the roles of these molecular components in the regulation of cognitive and brain function, in part due to the proposed central involvement of glutamate system dysfunction in a broad range of brain disorders with prominent cognitive deficits including schizophrenia (SZ) (Coyle, 2006), bipolar disorder (McCloud et al., 2015), major depressive disorder (deWilde et al., 2015), autism spectrumdisorders (Volk et al., 2015) and Alzheimer’s disease (Lin et al., 2014).

The role of the NMDA receptor in

cognition

NMDA receptors are tetrameric structures assembled from two obligatory GluN1 subunits (formerly NR1) and two GluN2 (GluN2A and GluN2D, formerly NR2A to NR2D) subunits. NMDA receptors may also contain GluN3 subunits, which are particularly abundant during early life and appear to have a role in limiting synapse maturation. The persistence

of GluN3A-containing NMDA receptors into adulthood may contribute to the synaptic dysfunction in psychiatric disorders

(Perez-Otano et al., 2016), while the potential role of GluN3B is yet to be elucidated. Differences in NMDA receptor subunit composition results in functional and pharmacological diversity, as exemplified by the differing pharmacology of GluN2A- versus GluN2B-containing NMDA receptors (Smith et al., 2011). The contribution of the different NMDA receptor subtypes

to cognition is relatively poorly defined. However, recent studies in genetically modified mice have proved useful in further elucidating the complex relationship that exists between NMDA receptors with specific subunit compositions, their cellular and brain region localization and distinct cognitive functions (Table 1). In addition to these studies a multitude of pharmacological studies conducted in rodents, non-human primates and human participants have characterized the role of the NMDA receptor in cognition. Here, we briefly review the general insights gained fromthese pharmacological

studies.

Evidence from pharmacological studies in rodents

The impact of acute NMDA receptor antagonist administration

Acute administration of NMDA receptor antagonists, such as ketamine, phencyclidine (PCP) and dizocilpine, has

been shown to negatively impact on domains of executive function in rodents, impairing cognitive flexibility (de Bruin

et al., 2013; Gastambide et al., 2013) and disrupting attentional processing (Amitai and Markou, 2010; Barnes et al.,

2016; Thomson et al., 2011). Acute NMDA receptor antagonist administration also negatively affects other cognitive domains impairing spatial reference learning and memory (for review, see Morris, 2013; Duan et al., 2013; Ihalainen et al.,

2016), short-term object recognition memory (Cloke and Winters, 2015; Rajagopal et al., 2016), associative memory (as assessed in the paired associates learning task, Kumar et al., 2015; Lins et al., 2015) and episodic learning and memory (Bast et al., 2005) in rodents. Acute NMDA receptor antagonist administration can also induce motivation deficits and motor impairments, which could potentially confound some of these cognitive measures (Noda et al., 2000). However, the impact of these drugs on cognitive performance can be assessed at doses and time points after administration where these confounding effects are absent. A key consideration in these acute NMDA receptor antagonist studies, as with all

pharmacological studies involving drugs targeting the glutamatergic system, is the importance of the temporal effects of

each compound. These effects may contribute to some of the different behavioural and neural effects observed between

different studies. Another concern is the non-selective pharmacology

of the compounds used. For example, PCP also acts

at nicotinic acetylcholine receptors (Fryer and Lukas, 1999)

and dopamine (D2) receptors (Seeman et al., 2009), while ketamine

binds to awide range of non-glutamatergic targets (for

review, see Mion and Villevielle, 2013). Thus, genetic studies

and studies using more pharmacologically selective compounds

have been instrumental in further supporting a key

role for the NMDA receptor in cognition.

The impact of prolonged NMDA receptor

hypofunction

A multitude of studies have characterized the effects of

prolonged NMDA receptor hypofunction (induced by repeated,

intermittent NMDA receptor antagonist treatment)

on various cognitive functions in rodents. Cognitive testing

in these studies is usually undertaken when animals are not

experiencing the acute effects of these antagonists (i.e. when

‘drug free’). Thus, the cognitive deficits present are thought to

result from the changes in plasticity that occur in the brain as

a result of prolonged NMDA receptor hypofunction. These

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effects on plasticity include modifications in the function of

non-glutamatergic neurotransmitter systems (Jentsch et al.,

1998; Lindefors et al., 1997), including the function of

parvalbumin-positive (PV+) GABAergic interneurons

(Bygrave et al., 2016), changes in synaptic plasticity (Nomura

et al., 2016), alterations in regional neuronal activity, including

prefrontal cortex (PFC) hypofunction (Dawson et al.,

2012), and altered brain network connectivity (see later discussion).

In these studies, prolonged NMDA receptor antagonism

has been shown to induce deficits in cognitive

Table 1

Cognitive deficits reported in genetic mouse models targeting the NMDA receptor

NMDA receptor

gene Mouse model Cognitive deficit Reference

GluN1 GluN1 hypomorphic mice Impaired spontaneous alternation Gregory et al., 2013

GluN1 hypomorphic mice Reduced spontaneous alternation Barkus et al., 2012

Impaired short-term object recognition

memory

Impaired spatial reference memory

Impaired learning in a visual

discrimination task

Ablation of GluN1 in cortical

excitatory neurons of mPFC

and SSCTX

Impaired short-term object recognition Rompala et al., 2013

Normal spatial working memory

Ablation of GluN1 in HP (DG

and CA1)

Impaired in spatial reversal learning

(water maze)

Taylor et al., 2014

Not impaired in spatial discrimination

(water maze)

GluN1 knockout in Parvalbumin

expressing interneurons

No deficit in cognitive flexibility,

working memory or attentional

processing

Bygrave et al., 2016

GluN2A GluN2A KO mice Impaired spatial working memory Bannerman et al., 2008

No impairment in long term spatial

reference memory

GluN2A KO mice Impaired extra-dimensional set shifting Marquardt et al., 2014

Not impaired in discrimination or

reversal learning

GluN2A KO in HP and CTX Impaired reversal learning Thompson et al., 2015

GluN2B GluN2B KO in principal neurons

of the postnatal forebrain

Impairment in spatial working memory,

spatial reference memory, impaired

recognition memory, performance

deficits in simple Morris water maze

and visual discrimination tasks

von Engelhardt et al., 2008

GluN2B KO in HP (CA1 and DG) Impaired spatial working memory and

reversal learning

von Engelhardt et al., 2008

No impairment in spatial reference

memory

GluN2C GluN2C KO mice Deficit in fear conditioning and spatial

working memory

Hillman et al., 2011

No impairment in spatial reference

memory

GluN2D GluN2D KO mice Impaired social memory Yamamoto et al., 2017

No impairment in novel object

recognition

GluN3A GluN3A KO mice Improved spatial learning and

enhanced object recognition memory

Mohamad et al., 2013

GluN3B GluN3B KO mice No difference in spatial reference

memory and fear conditioning

Niemann et al., 2007

CA1, cornu ammonis 1 subfield; CTX, cortex; DG, dentate gyrus; HP, hippocampus; KO, knock-out; mPFC, medial prefrontal cortex; SSCTX, somatosensory

cortex.

M R Dauvermann et al.

flexibility (Dawson et al., 2012; McLean et al., 2012), attentional

processing (Thomson et al., 2011; Barnes et al., 2016),

spatial reference learning and memory (Didriksen et al.,

2007), working memory (Seillier and Giuffrida, 2009) and

short-term object recognition memory (Pyndt Jorgensen

et al., 2015; Horiguchi et al., 2013; Rajagopal et al., 2016).

While the translational relevance of some of these behavioural

tests to aspects of human cognition is questionable

(Kas et al., 2014; Pratt et al., 2012; Pryce and Seifritz, 2011),

the overall findings indicate a central role for the NMDA receptor

in a broad range of cognitive processes.

In addition to these studies, conducted in adult animals,

the impact of pharmacologically-induced NMDA receptor

hypofunction at specific developmental time points (either

in utero, during early postnatal development or during

adolescence) on cognitive function in the fully developed

animal has also been assessed (Broberg et al., 2008; Li et al.,

2011; Zhao et al., 2014). These studies highlight the

neurodevelopmental role of NMDA receptor activity, at

defined epochs of brain development, in ‘setting up’ the brain

for effective cognitive function. This area of research certainly

warrants further systematic investigation.

Insights from studies using NMDA receptor

subtype selective drugs

Pharmacological studies have also attempted to elucidate the

role of specific NMDA receptor subtypes in cognition. For example,

the distinct pharmacology of GluN2A versus

GluN2B-containing NMDA receptors has allowed the recent

characterization of the role of these receptor subtypes in different

cognitive functions. The GluN2A-selective antagonist

NVP-AMM077 has recently been shown to decrease accuracy

in a task assessing sustained attention (5-choice serial reaction

time task, 5-CSRTT; Smith et al., 2011), but has little effect

on location discrimination, paired-associate learning

and working memory (as assessed using the trial-unique, delayed

nonmatching to location (TUNL) task; Kumar et al.,

2015). In contrast, GluN2B-selective antagonists, such as Ro

25-6981 and traxoprodil, appear to improve accuracy and

processing speed in the 5-CSRTT (Higgins et al., 2005; Smith

et al., 2011). However, antagonism of GluN2B using

ifenprodil has been shown to impair performance in response

time (RT) in the 5-CSRTT (Higgins et al., 2005). This

conflicting finding, compared with the effects of other

GluN2B antagonists, may be due to non-selective actions of

ifenprodil or its relative weak affinity for GluN2B-containing

NMDA receptors. Further NMDA receptor subtype-specific

effects are supported by the observation that traxoprodil

administration impairs location discrimination but not working

memory in the TUNL task (Kumar et al., 2015). In

addition, Ro 25-6981 ameliorates the effect of ketamine treatment

on cognitive flexibility (assessed using the attentional

set-shifting task (ASST), Kos et al., 2011), supporting a

primary role for GluN2B-containing NMDA receptors in the

effect of ketamine on cognitive flexibility.

There are a lack of studies reporting the cognitive impact

of GluN2C and GluN2D-selective compounds. While

GluN2C/D-selective compounds, such as the inhibitor

DQP-1105 (Acker et al., 2011), are available, their effects on

cognition have not yet been tested. However, evidence for

the role of GluN2C/D-containing NMDA receptors in cognitive

function is supported by studies conducted in genetically

modified mice (Table 1). In addition, GluN2C/D-containing

NMDA receptor play an important role in the effects of the

NMDA receptor antagonists ketamine and memantine

(Kotermanski and Johnson, 2009), which may include their

effects on cognitive functions. In addition, the absence of

either GluN2C or GluN2D receptors has been shown to have

different effects on the cortical oscillations induced by NMDA

receptor blockade (Gupta et al., 2016; Sapkota et al., 2016).

Other evidence supporting a role for GluN2C/D-containing

NMDA receptors in cognitive function comes from studies

using positive allosteric modulators (PAMs), such as CIQ

and D-cycloserine, discussed later in this review.

Insights from studies in genetically modified

mice

A range of studies have used genetically modified mice to further

determine the role of the different NMDA receptor subtypes

in a range of cognitive functions (Table 1). These studies

are often able to extend the understanding gained from relevant

pharmacological studies, in part due to the greater assurance

of NMDA receptor subtype specificity, but also by

targeting either specific brain subsystems (GluN1; Rompala

et al., 2013; Taylor et al., 2014) or cell populations (GluN1 in

PV+ interneurons; Bygrave et al., 2016). A limitation of these

genetic studies is the neurodevelopmental role ofNMDA receptors

in the development of effective cognitive function, as

highlighted by the persistent effects of non-selective NMDA receptor

antagonists when selectively administered at specific developmental

time points (Broberg et al., 2008; Li et al., 2011;

Zhao et al., 2014). Thus, the observed effects may be very different

from those elicited by acute pharmacological regulation of

these receptor subtypes. Nevertheless, studies using both genetic

and pharmacological approaches offer complementary

strategies to further elucidate the role of specific NMDA receptors

subtypes in cognition, with modern genetic approaches offering

new levels of granular neural system, temporal and celltype

resolution.

The NMDA receptor hypofunction

hypothesis of schizophrenia

The ‘glutamate hypothesis of SZ’ posits that a dysfunctional

glutamatergic system is a key pathophysiological mechanism

contributing to the clinical symptoms seen in patients with

SZ (Luby et al., 1959; Carlsson et al., 2000; Farber et al.,

2002; Javitt, 2007; Javitt et al., 2012). The ‘NMDA receptor

hypofunction hypothesis of SZ’, a more specific theory of

the glutamate dysfunction hypothesis, has its origins in the

observation that acute administration of NMDA receptor antagonists,

such as ketamine and PCP, induces psychotic-like

symptoms (delusions and hallucinations) in healthy controls

(HCs) that are similar to those seen in patients with SZ

(Krystal et al., 1994; Abi-Saab et al., 1998). In addition, individuals

who chronically abuse PCP (presumably inducing repeated

intermittent NMDA receptor hypoactivity) show

deficits in executive function similar to those seen in patients

with SZ (Cosgrove and Newell, 1991). These observations

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have led to the development of two distinct but overlapping

models of the glutamate hypothesis of SZ: (i) the ‘prolonged

NMDA receptor hypofunction model’ and (ii) the ‘acute

NMDA receptor hypofunction model’.

The ‘prolonged NMDA receptor hypofunction model’ postulates

that prolonged hypoactivation of theNMDA receptor induces

multiple pathological mechanisms involved in the

disorder (Coyle, 2006; Coyle et al., 2010; Moghaddam and

Krystal, 2012; Javitt et al., 2012) and that NMDA receptor

hypofunction may be the final pathophysiological pathway

for the positive, negative and cognitive symptoms experienced

by patients with SZ (Carlsson et al., 1999; Goff and Coyle,

2001; Coyle, 2006; Javitt, 2010; Balu and Coyle, 2015). The

‘acute NMDA receptor hypofunction model’ originates from

clinical trials when ketamine was administered to HCs. Early

findings found that changes in glutamatergic signalling could

explain the psychotomimetic effects of ketamine and PCP in

terms of the positive symptoms present in individuals with first

episode SZ (FES) or first episode psychosis (Krystal et al., 1994;

Krystal et al., 1999; Khlestova et al., 2016). While the findings

from the acute ketamine administration model have particularly

increased our understanding of the positive and negative

symptoms seen in patients with SZ, evidence for translationally

relevant alterations in cognitive functions is more limited. We

describe some of these exemplary cognitive studies below and

outline their translational alignment to observations made in

patients with SZ.

Evidence from pharmacological studies

in human participants

In HCs, acute ketamine administration has been shown to

significantly affect a range of cognitive functions, with the effects

being similar to those seen in patients with SZ. Low-dose

ketamine administration (100 ng·mL\_1 of plasma) affects

contingency learning in HCs when assessed using a probabilistic

learning task (Vinckier et al., 2016), with ketamine administration

inducing misleading cue-outcome associations.

These findings contrast with those reported in an early study

where the same dose of ketamine (100 ng·mL\_1 of plasma)

failed to alter task performance (Corlett et al., 2006). However,

in both studies similar effects of ketamine on blood oxygen

level-dependent (BOLD) responses (increased) were

observed in regions of the PFC of participants undertaking

the task. Deficits in contingency learning as well as increased

BOLD responses in the PFC have also been reported in

patients with SZ (Diaconescu et al., 2011). However, decreased

BOLD responses in the PFC of patients with SZ during

contingency learning have also been reported (Dowd et al.,

2016). In addition, increased BOLD responses in a range of

other brain regions have also been reported in SZ patients undertaking

this task (Diaconescu et al., 2011; Park et al., 2015;

White et al., 2015) that are different from those seen in

ketamine functional MRI (fMRI) studies in HCs. It is important

to note that different temporal effects of drug administration

may contribute to some of the diverse findings in

behavioural performance and neural function reported in

these clinical studies.

Ketamine administration has also been shown to significantly

affect working and declarative memory in HCs.

Ketamine administration significantly reduced accuracy in

the continuous performance task (CPT) and impaired both

immediate and delayed recall in the Hopkins verbal learning

task (Krystal et al., 2005). The effect of ketamine on working

memory function was confirmed by another study (Honey

et al., 2008). The effects of ketamine on working and declarative

memory tasks are similar to those seen in patients with SZ

(Blokland et al., 2017; Green, 2016). However, the impact of

ketamine on BOLD responses during working memory and

declarative memory tasks in HCs is more difficult to corroborate

with the fMRI findings seen between SZ patients and HC,

where both increased and reduced BOLD responses are observed

in patients with SZ when compared with HCs (Brown

and Thompson, 2010; Dauvermann et al., 2014). While

Anticevic et al. (2012) and Driesen et al. (2013) reported reduced

BOLD responses in the dorsolateral PFC (DLPFC) and

precuneus in HCs treated with ketamine and SZ patients during

working memory performance, the findings by Honey

et al. (2008) (increased BOLD responses in the basal ganglia

and thalamus of HC treated with ketamine during the task)

are more difficult to align with the observations made in patients

with SZ.

Ketamine administration has also been shown to affect attentional

processing, when assessed using both visual and auditory

tasks. In HCs, ketamine was found to significantly

reduce the response time (RT) to target stimuli in a visual oddball

task assessing attentional processing (Watson et al.,

2009), an effect that is similar to the reduced visual processing

speed seen in patients with SZ (Urban et al., 2008). Similarly,

in HCs, ketamine (0.24 mg·kg\_1) also affects

attentional processing when assessed using an auditory processing

task, increasing the number of false alarms during

the task (Umbricht et al., 2000). In addition, in this study, ketamine

administration was also found to reduce the peak amplitude

of the mismatch negativity (MMN) signal, an aspect

of the event-related potential detected using EEG that is

indicative of the arrival of an odd stimulus in a sequence of

stimuli. Similar cognitive effects were independently observed

when using both a low and high dose of ketamine,

with only the higher dose inducing significant deficits in

MMN (Heekeren et al., 2008). The deficits in auditory attentional

processing and MMN seen during ketamine administration

are similar to those reported in patients with SZ

(Milovan et al., 2004). Summary outlines of these studies are

provided in Table 2.

The impact of NMDA receptor

co-agonists and partial agonists on

cognition

Much research has been dedicated to elucidate the

procognitive potential of activating NMDA receptors, with

positive modulation rather than agonism (which risks inducing

excitotoxicity) being a key area of research. The glycine

site on the NMDA receptor provides an attractive drug target

because of its positive modulatory effects on NMDA receptor

signalling. The amino acid derivatives D-serine and

D-cycloserine act as partial agonists at this site (Mothet

et al., 2000; Watson et al., 1990). The therapeutic potential

Table 2

Impact of NMDA receptor antagonist administration on cognitive functions in human controls

Study (year)

Experimental group/

patient group

Control group/control

matching criteria

Study design/Drug

administration

Task design for

cognitive function

Main findings – effects of

drug on cognition and/or

neural response measures

during cognition

N

(M : F)

Mean age

in years (SD)

N

(M : F)

Mean age in

years (SD)

Contingency learning

Vinckier et al.,

2016

N/A HCs

21 (11:10) 28.7 (±3.2)

• Double-blind, placebocontrolled,

randomized,

within-subjects study design

• Two separate drug challenge

sessions (placebo/active

drug):

• Ketamine: low-dose bolus

and i.v. injection

• Placebo: Saline

fMRI:

Probabilistic learning

task – parametric

modulation.

1 GLM: Separation

of categorical

regressors for cue

and outcome onsets

2 GLM:Outcome

onsets modulated

by two computational

variables (ROI analysis)

Effect of ketamine on cognitive

performance:

• Ketamine decreases

optimization of outcomes

given misleading unexpected

outcomes

Effect of ketamine on BOLD

response:

• Altered BOLD response in

fronto-parietal regions based

on contingency learning,

mostly in regions of the

cerebellum, MFG, DLPFC and

inferior parietal cortex in

ketamine when compared to

placebo (ROI analysis)

Corlett et al.,

2006

N/A HCs

15 (8:7)

29 (±7)

• Double-blind, placebocontrolled,

randomized,

within-subjects study design

• Two separate drug challenge

sessions (placebo/active drug):

• Ketamine: low-dose bolus and

i.v. Injection while in scanner

• Ketamine: high-dose bolus

and i.v. injection outside of

• Placebo: Saline

fMRI:

Associative learning

task.

• Associative

relationships

• Prediction error

Effect of ketamine on cognitive

performance:

• No difference in behavioural

performance between

ketamine and placebo

Effect of ketamine on BOLD

response:

continues

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Table 2 (Continued)

Study (year)

Experimental group/

patient group

Control group/control

matching criteria

Study design/Drug

administration

Task design for

cognitive function

Main findings – effects of

drug on cognition and/or

neural response measures

during cognition

N

(M : F)

Mean age

in years (SD)

N

(M : F)

Mean age in

years (SD)

• Increased BOLD response in

the right PFC in response

to expected stimuli in

ketamine when compared

to placebo (prediction error)

Working memory and declarative memory

Krystal et al.,

2005

N/A HCs – Amphetamine

group (14 study

completers)

HCs – Ketamine

group (13 study

completers)

27 (16:11)

16 Male 33(±8.9)

11 Female 28(±5.2)

• Double-blind, randomized,

placebo-controlled, study

design

• Amphetamine group:

1) Infusion of 0.25 mg·kg\_1

followed by saline,

2) Ketamine infusion of

0.23 mg·kg\_1,

3) Amphetamine placebo

(saline), 4) Ketamine,

5) Placebo amphetamine,

6) Placebo ketamine.

• Ketamine group: Same

idea as above but swapped

between amphetamine

and ketamine

1 CPT

2 HVLT (6 versions)

3 PANSS:Cognitive

symptom score.

Effect of ketamine on cognitive

performance:

1 Significant effect in accuracy

on CPT for ketamine but not

for amphetamine.

2 For HVLT immediate recall,

there was a significant

interactive effect of ketamine

with amphetamine when

compared to placebo.

2. For HVLT delayed recall,

there was a significant

interaction between ketamine

and amphetamine.

Honey et al.,

2008

N/A HCs

15 (8:7) 29 (±7)

• Double-blind, placebocontrolled,

randomized,

within-subjects study design

• Two separate drug challenge

sessions (placebo/active drug):

• Ketamine: low-dose bolus and

i.v. Injection while in scanner

• Ketamine: high-dose bolus

and i.v. injection outside of

• Placebo: Saline

fMRI:

1 Working memory

(N-Back task). Button

presses for targets and

distractors.

2 CPT (Button press for

targets but not for

distractors)

3 Sentence completion

task (Button press for

task completion)

4 Verbal self-monitoring

task (Sub-vocalization

Effect of ketamine on cognitive

performance:

1 Significant effect of ketamine

for RT compared to placebo.

2 Significant effect of ketamine

for RT compared to placebo.

Effect of ketamine on BOLD

response;

1 Increased BOLD response of

basal ganglia and thalamus

continues

Table 2 (Continued)

Study (year)

Experimental group/

patient group

Control group/control

matching criteria

Study design/Drug

administration

Task design for

cognitive function

Main findings – effects of

drug on cognition and/or

neural response measures

during cognition

N

(M : F)

Mean age

in years (SD)

N

(M : F)

Mean age in

years (SD)

during sentence

completion and

incompletion)

after ketamine across all

working memory load

conditions with a strong

effect for 2-Back (ROI

analysis)

2 No effect of ketamine

observed.

3 No effect of ketamine

observed.

4 No effect of ketamine

observed.

Anticevic

et al., 2012

N/A HC – Ketamine

group

19 (10:9)

27.5 (±6.3)

• Double-blind, placebocontrolled,

randomized,

within-subjects study design

• Three separate drug challenge

sessions (placebo/active drug):

• Ketamine: i.v. via initial bolus

0.23 mg·kg\_1 over 1 min,

followed by subsequent

infusion (0.58 mg·kg\_1

over 1 h)

• Placebo: 1 saline injection

fMRI (FC):

Delayed spatial

working memory

task

Effect of ketamine on

cognitive performance:

• Decreased accuracy for

working memory versus

control trials under

ketamine

Effect of ketamine on

BOLD response;

• Ketamine attenuated taskbased

activations of the

DLPFC and precuneus for

the working memory task

and task-based deactivations

for the DMN.

continues

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Table 2 (Continued)

Study (year)

Experimental group/

patient group

Control group/control

matching criteria

Study design/Drug

administration

Task design for

cognitive function

Main findings – effects of

drug on cognition and/or

neural response measures

during cognition

N

(M : F)

Mean age

in years (SD)

N

(M : F)

Mean age in

years (SD)

Effect of ketamine on FC;

• Seed-based FC for the seed

regions as part of the frontoparietal

and the DMN:

Significant modulation of

the task-based FC (delay

part of the working memory

task) and DMN under

ketamine

Driesen et al.,

2013

N/A HCs – Ketamine

group

22 (14:8)

not reported

• Double-blind, placebocontrolled,

randomized,

within-subjects study design

• Three separate drug challenge

sessions (placebo/active drug):

• Ketamine: i.v. via initial bolus

0.23 mg·kg\_1 over 1 min,

followed by subsequent

infusion (0.58 mg·kg\_1

over 1 h)

• Placebo: 1 saline injection

fMRI (FC):

Spatial ‘2-Back’ and

‘4-Back’ conditions.

1 Seed-based crosscorrelation

2 Global-based

connectivity

Effect of ketamine on cognitive

performance:

• Decreased accuracy for

working memory versus

control trials under ketamine

Effect of ketamine on BOLD

response;

• Ketamine attenuated taskbased

activations of the

DLPFC and precuneus for

the working memory task

and task-based deactivations

for the DMN.

Effect of ketamine on FC;

1 Decreased FC between right

DLPFC and MFG, IFG under

ketamine when compared

to placebo

continues

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Table 2 (Continued)

Study (year)

Experimental group/

patient group

Control group/control

matching criteria

Study design/Drug

administration

Task design for

cognitive function

Main findings – effects of

drug on cognition and/or

neural response measures

during cognition

N

(M : F)

Mean age

in years (SD)

N

(M : F)

Mean age in

years (SD)

2 Decreased FC within the

left DLPFC

Braun et al.,

2016

N/A HCs – Dextromethorphan

group

37 (30:7)

25.3(±4.2)

• Double-blind, placebocontrolled,

randomized,

cross-over study design

• Two separate drug challenge

sessions (placebo/active drug):

• Dextromethorphan: 120 mg

in capsule form

• Placebo: capsule

fMRI (FC):

N-Back working

memory task (0-Back

and 2-Back conditions),

Button presses for the

target stimuli

Effect of dextromethorphan

on cognitive performance:

• No differences for accuracy

or RT in the working memory

task between dextromethorphan

versus placebo

Effect of dextromethorphan

on FC;

• FC for 270 regions in terms

of network flexibility:

Increased network flexibility

under dextromethorphan when

compared to placebo

Visual attentional processing

Watson

et al., 2009

N/A HC

23 (15:8)

24.55 (±2.59)

• Double-blind, placebocontrolled

study design

• Three separate drug

challenge sessions:

• Saline (placebo)

• Ketamine (0.23 mg·kg\_1 and

infusion rate: 0.58 mg·kg\_1·h\_1)

• Thiopental (1.5 mg·kg\_1 and

infusion rate: 40mcg·kg\_1·h\_1)

EEG/ERP:

3-stimulus visual

oddball task

Effect of ketamine on thiopental

on cognitive performance:

• Decreased target RT after

thiopental and ketamine when

compared to placebo; stronger

effect in thiopental

• Effect of ketamine and thiopental

on ERPs:

• Decreased target P3b amplitude

at electrode Pz after ketamine

versus placebo

continues

Glutamate cognition and networks **BJP**

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Table 2 (Continued)

Study (year)

Experimental group/

patient group

Control group/control

matching criteria

Study design/Drug

administration

Task design for

cognitive function

Main findings – effects of

drug on cognition and/or

neural response measures

during cognition

N

(M : F)

Mean age

in years (SD)

N

(M : F)

Mean age in

years (SD)

• Decreased target P3b amplitude

at electrode Pz after thiopental

versus placebo

• No difference in target P3b

amplitude between ketamine

and thiopental

• Significant correlations

between changes in P3b

amplitude and target RT after

thiopental but not ketamine

at electrode Pz

Auditory attentional processing

Umbricht

et al., 2000

N/A HCs

20 (14:6)

24.6(±2.9)

• Double-blind, placebocontrolled

study design

• Two separate drug challenge

sessions (placebo/active drug):

• Ketamine: (0.24 mg·kg\_1 and

infusion rate: 0.0 mg·kg\_1·h\_1)

• Placebo: Physiological

sodium chloride solution

and 5% glucose

EEG/ERP

Visual AXE-CPT during

the auditory test

paradigm (MMN)

Effects of ketamine on cognitive

performance:

• Decreased correct detection

of hits after ketamine

administration compared

to baseline

• Increased false alarms after

ketamine administration

compared to baseline and

placebo conditions

Effects of ketamine on

auditory ERPs:

• Decreased peak amplitudes

of MMN after ketamine in

pitch-deviance condition and

duration-deviance condition

compared to baseline condition

and placebo condition respectively.

continues

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Table 2 (Continued)

Study (year)

Experimental group/

patient group

Control group/control

matching criteria

Study design/Drug

administration

Task design for

cognitive function

Main findings – effects of

drug on cognition and/or

neural response measures

during cognition

N

(M : F)

Mean age

in years (SD)

N

(M : F)

Mean age in

years (SD)

• Increased N1 peak amplitude after

ketamine administration compared

to placebo

Heekeren

et al., 2008

N/A HCs

15 (9:6)

38 (not reported)

• Randomized, doubleblind,

cross-over study

design

• Low and high dose

of the 5HT2A agonist

DMT

• Low and high dose

of S-ketamine

EEG/ERP

Visual AXE-CPT

during the auditory

test paradigm (MMN)

Effects of ketamine on cognitive

performance:

Low-doses and high-doses of DMT

and S-ketamine impair behavioural

performance during the AXE-CPT

Effects of ketamine on auditory ERPs:

• Decrease in generation of MMN

after S-ketamine > DMT

• Trend decrease in the frequencydeviant-

induced MMN at

electrode Fz after low-dose

S-ketamine

• Decreased duration-deviant

MMN at electrodes Fz, F3, F4

after low-dose and high-dose

S-ketamine

BOLD, blood oxygen level-dependent; CPT, continuous performance task; DLPFC, dorsolateral prefrontal cortex; DMN, default-mode network; DMT, dimethyltryptamine; EEG, electroenchephalogram; ERP,

event-related potential; FC, functional connectivity; fMRI, functional magnetic resonance imaging; HVLT, Hopkins verbal learning test; IFG, inferior frontal gyrus; i.v., intravenous;MFG,middle frontal gyrus; N/A,

not applicable; PANSS, positive and negative symptoms scale; ROI, region of interest; RT, response time.

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of NMDA receptor-positive modulators in SZ patients has

been reviewed previously (Kantrowitz and Javitt, 2010; Balu

and Coyle, 2015; Goff, 2012). Here, we highlight and discuss

recent findings of rodent and human studies featuring these

drugs with a particular focus on cognition and, where applicable,

summarize neuroimaging findings from rodent and

human studies.

Pharmacological studies in rodents

In rodent studies, both D-serine and D-cycloserine have

been shown to have procognitive effects. For example,

D-cycloserine improves short-term object recognition,

potentiates contextual and cued fear extinction learning in

rats (Sugiyama et al., 2015; Walker et al., 2002) and improves

spatial learning in aged rats (Baxter et al., 1994). In addition,

intrahippocampal D-cycloserine administration has been

shown to reverse dizocilpine-induced impairments in working

memory performance in the radial arm maze (Kawabe

et al., 1998), suggesting that D-cycloserine administration

can reduce the impact of acute NMDA receptor hypofunction

on working memory. Similar effects have been shown for

D-serine, which improves working memory performance

in the T-maze alternation test and enhances novel object

recognition, while also reversing the long-term memory

deficits induced by dizocilpine (Bado et al., 2011). In addition,

the recently developed tetrapeptide rapastinel (also

known as GLYX-13), a partial agonist of the NMDA receptor

glycine site, has also been shown to improve learning

and memory in young and aged rats (Burgdorf et al., 2011) as

well as restoring object recognition in mouse models of acute

and prolonged NMDA receptor hypofunction (Rajagopal

et al., 2016).

D-cycloserine demonstrates greatest efficacy at NMDA

receptors containing GluN2C subunits (Ogden et al., 2014),

suggesting a central role for this NMDA receptor subtype

in its procognitive effects. Potentiation of GluN2C/Dcontaining

NMDA receptors using CIQ has been shown to facilitate

fear learning and extinction in mice (Ogden et al.,

2014) and reverses the deficit in working memory (spontaneous

alternation test) in mice following acute dizocilpine administration

(Suryavanshi et al., 2014). A role for GluN2C

subunit-containing NMDA receptors in working memory is

further supported by observations in GluN2C knockout mice

(Hillman et al., 2011, Table 1). Interestingly, these mice do

not show deficits in spatial reference memory, which contrasts

with the ability of D-cycloserine to improve spatial

reference memory in aged rats (Baxter et al., 1994). This

suggests that the activity of D-cycloserine at other NMDA

receptor subtypes may be more important for its effects on

spatial reference memory or that developmental adaptations

prevent the effect of GluN2C knockout on spatial reference

memory in GluN2C knockout mice.

Evidence from pharmacological studies

in humans

In contrast to the results of rodent studies, which support the

procognitive potential of NMDA receptor partial agonism,

the evidence from studies in humans, including studies in patients

with SZ, is less persuasive. In HCs, glycine

administration does not improve general cognitive performance

on the CogState test battery (Neumeister et al., 2006)

or in a visual attention task (O’Neill et al., 2011). Furthermore,

D-cycloserine administration does not improve motor

sequence learning in HCs (Gunthner et al., 2016). In contrast,

initial studies undertaken in a small sample of 12 HC males

support a significant effect of the glycine transporter inhibitor

Org 25935 on verbal learning and delayed recall, but not

on any of the other cognitive tests employed (D’Souza et al.,

2012). More recently, Org 25935 administration was also

shown not to improve performance in a visuo-spatial task, a

workingmemory task or a verbal memory task in HCs (Christmas

et al., 2014). This suggests that the procognitive potential

of these compounds in HCs may be limited. Given that

NMDA receptor functionmay be optimal in HCs, it is not surprising

that these compounds fail to significantly improve

cognitive performance in these studies. Despite these findings,

one might still predict that these compounds would

have procognitive potential in patients with brain disorders

thought to involve NMDA receptor hypofunction, such as

patients with SZ. However, studies investigating the

procognitive potential of drugs that positively modulate

NMDA receptor activity in patients with SZ are negative overall.

For example, D-cycloserine adjunctive treatment does not

improve composite scores of general cognitive function or

most individual cognitive domain scores when assessed using

standardized neuropsychological batteries, in patients with

established SZ (EST) (Buchanan et al., 2007; Goff et al., 2005;

Goff et al., 2008; Weiser et al., 2012; Cain et al., 2014). Dcycloserine

treatment also fails to improve performance in

the CPT and working memory tasks in patients with EST

(Duncan et al., 2004). However, there are also positive findings

where D-cycloserine improved cognitive performance

following a cognitive remediation programme in patients

with EST (Cain et al., 2014) and D-cycloserine has been

shown to facilitate fear extinction therapies in people with

anxiety disorders (Norberg et al., 2008). These findings suggest

that D-cycloserine may yet hold therapeutic value as it

can potentiate the efficacy of cognitive behavioural therapies,

at least in some cognitive domains. Despite this suggestion,

overall findings from recent meta-analysis do not

support the procognitive efficacy of compounds potentiating

NMDA receptor activity in SZ. While Tsai and Lin (2010)

found a positive impact of NMDA receptor enhancing agents

(D-cycloserine, glycine and sarcosine) on cognitive symptoms

in patients with SZ (assessed using the positive and negative

symptoms scale cognitive subscale), two more recent

meta-analyses found no effect (Choi et al., 2013; Iwata et al.,

2015). Choi et al. (2013) found that D-cycloserine, D-serine

and the AMPA receptor PAM CX516, when used as adjunctive

treatments, did not significantly improve function in five

cognitive domains (Choi et al., 2013). Furthermore, Iwata

et al. (2015) found that NMDA receptor glycine site drugs

had no significant effect in eight cognitive domains. Thus,

any procognitive effects of NMDA receptor glycine site modulators

in patients with SZ are yet to be robustly established.

One reason for the disparity between preclinical and clinical

studies may be the testing of these compounds as adjunctive

treatments in patients, as their procognitive efficacy has not

been tested in the context of prolonged antipsychotic administration

preclinically (a summary of the information from

**BJP**

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Table 3

Impact of NMDA receptor coagonists and partial agonists on cognition

Study (year)

Experimental group/

patient group phase

of SZ

Control group/control

matching criteria

Study design/drug

administration

Task design for

cognitive function

Main findings – effects of drug

on cognition and/or neural

response measures during

N (M : F) cognition

Mean age

in years (SD) N (M : F)

Mean age

in years (SD)

General cognition

Goff et al.,

2005

EST- D-cycloserine group

(adjunctive treatment)

27 (24:3) 45.9(±7.4)

EST – placebo group

28 (20:8) 47.0(±8.6)

N/A • Randomized doubleblind,

placebo-controlled,

parallel group study design

• 6 month trial

• D-Cycloserine: 50 mg

capsule at bedtime in

adjunct with conventional

antipsychotic medication

• Placebo: capsule at bedtime

in adjunct with conventional

antipsychotic medication

Cognitive battery:

1 CVLT

2 IQ estimation (Vocabulary,

Information, Digit Span

and Block Design)

3 ANART

4 Stroop Test

5 Categories

6 Finger Tapping

7 WCST

Effect of D-Cycloserine on cognitive

performance:

• No difference between treatment

groups on any cognitive task at

weeks 8, 12 and 24 compared

to baseline.

Neumeister

et al., 2006

N/A HCs

12 (8:4) 28.5(±10.5)

• Double-blind, randomized,

balanced cross-over study

design

• Two separate drug challenge

sessions (placebo/active drug):

• Glycine: 200 mg·kg\_1 body

weight for 45 min i.v.

• Placebo: saline

Neuropsychological testing

outside of PET scanner:

1 CogState computerized

battery (i.e. attention, visual,

verbal and working memory,

executive function, speed

of processing)

Effect of glycine on cognitive

performance:

• No significant effect of glycine

on any of the neuropsychological

tests compared to placebo

Effect of glycine on PET measures:

• Decreased whole-brain cerebral

metabolic rate of glucose

(CMRGlu) in glycine treated

HCs when compared to placebo

• Decreased rCMRGlu in cerebellum

and DLPFC without whole-brain

correction (ROI analysis)

Buchanan

et al., 2007

EST – D-cycloserine group

53 (not reported) 44.4

(±10.4)

N/A • 16 week double-blind,

double-dummy, parallel

Battery: Effect of glycine on cognitive

performance:

continues

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Table 3 (Continued)

Study (year)

Experimental group/

patient group phase

of SZ

Control group/control

matching criteria

Study design/drug

administration

Task design for

cognitive function

Main findings – effects of drug

on cognition and/or neural

response measures during

N (M : F) cognition

Mean age

in years (SD) N (M : F)

Mean age

in years (SD)

EST – glycine group

(adjunctive treatment)

52 (not reported) 42.6

(±10.8)

EST –placebo group

52 (not reported) 43.4

(±11.4)

group, randomized study

design

• Three treatment groups

(pill-based):

• Active glycine + placebo

D-cycloserine

• Placebo glycine + active

D-cycloserine

• Placebo glycine + placebo

D-cycloserine

1 Processing speed

2 Verbal fluency

3 Motor speed

4 Vigilance

5 Auditorymemory

6 Visual spatial memory

7 Auditory working memory

8 Visuo-spatial working

memory

9 Executive function

• No difference between glycine

and placebo on the composite

cognition summary score

• No significant glycine/placebo

or D-cycloserine/placebo

differences

Liem-Moolenaar

et al. 2010

N/A HCs

45 (45:0) 18–55

Four treatment

groups of 15

subjects in each

• Double-blind, placebocontrolled,

four-period

cross-over ascending dose

study design

• Scopolamine 0.5 mg or

placebo i.v. for 15 min

and 0, 3, 10, 30 mg of

R213129 or placebo

oral administration

Adaptive tracking, finger

tapping, Stroop test, VVLT

Effect of scopolamine on cognitive

performance:

• Decrease in all parameters of

VVLT with scopolamine when

compared to placebo

• Decrease in all parameters of

the Stroop test with scopolamine

when compared to placebo

Weiser

et al., 2012

EST – D-serine group

(adjunctive treatment)

97 (74:23) 39.39 (±12.0)

EST – placebo group

98 (70:28) 39.75(±12.3)

N/A • 16 week double-blind,

randomized, placebocontrolled

study design

• Over course of study

between 1.6 g.day-1 and

2 g.day-1 of D-serine

Hebrew version of the

MATRCIS with 10 subtests

Effect of D-serine on cognitive

performance:

• No effect of treatment group

or group-by-time interaction

for the composite score and the

individual scores

Cain et al.,

2014

EST – D-Cycloserine group

(adjunctive treatment)

18 (16:2) 48.8(±11.5)

EST – Placebo group

18 (15:3) 46.2(±13.3)

N/A • 8 week single-blind,

randomized, placebocontrolled

study design

• D-cycloserine 50 mg.week-1

or placebo (capsule)

• Cognitive Remediation

between 3–5 timed

weekly – Brain Fitness Programme

• Auditory discrimination

training

• MATRICS

neuropsychological test battery

Effect of D-Cycloserine on cognitive

performance:

• No difference in auditory

discrimination training in

D-Cycloserine when compared

to placebo at baseline

• Increase in auditory discrimination

training in D-Cycloserine when

compared to placebo at each visit

after baseline

continues

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Table 3 (Continued)

Study (year)

Experimental group/

patient group phase

of SZ

Control group/control

matching criteria

Study design/drug

administration

Task design for

cognitive function

Main findings – effects of drug

on cognition and/or neural

response measures during

N (M : F) cognition

Mean age

in years (SD) N (M : F)

Mean age

in years (SD)

• No difference in the composite sore

or individual scores of the MATRICS

in D-Cycloserine when compared

to placebo

• Increase in composite score and

individual scores of some MATRICS

tests in placebo when compared to

D-Cycloserine

Christmas

et al., 2014

N/A HCs – Org 25 935 group

16 (16:0) 23.8

(± not reported)

HCs – placebo group

16 (16:0) 25.3

(± not reported)

• Double-blind, randomized,

placebo-controlled, parallel

group, single-dose study

design

• Org 25 935: Oral dose

of 12 mg

• Matching placebo

• Visuo-spatial cognitive

task (Manikin task)

• Digit span

• Verbal memory task

Effect of Org 25925 on cognitive

performance:

• No difference between the groups

in the Manikin task or any of the

other tasks

Working memory

Duncan

et al., 2004

EST – D-Cycloserine

group

(adjunctive treatment)

10 (10:0) 48.7 (±5.1)

EST- placebo group

12(12:0) 54.5(±6.8)

N/A • 4-week double-blind,

randomized, parallelgroup

study design

• D-cycloserine: 50 mg

(capsule) or placebo

(capsule)

1. AXE-CPT

2. Sternberg Short Term

Memory Scanning

Paradigm

• At baseline, after 2 weeks

and 4 weeks

• In subgroup of 7 EST in

the D-cycloserine group

and 8 in the placebo group

Effect of D-cycloserine on cognitive

performance:

• No differences in accuracy or RT

on the CPT between D-cycloserine

and placebo at all three time points

• No differences in accuracy or RT on

the Sternberg test between

D-cycloserine and placebo at all

three time points

ANART, Adult North American Reading Test; CVLT, California Verbal Learning Test; CPT, continuous performance test; HC, healthy control; HVLT, Hopkins Verbal Learning Test; IQ, intelligence quotient;

MATRICS, measurement and treatment research to improve cognition in schizophrenia; N/A, not applicable; PANSS, positive and negative symptoms scale; PET, positron emission tomography;

WCST, Wisconsin Card Sorting Test; VVLT, visual verbal learning test.

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these studies is presented in Table 3). Furthermore, clinical efficacy

has only been tested in patients with EST, and whether

these drugs would be beneficial during earlier stages of the

disease, such as in FES patients, has not yet been adequately

tested. The temporal relevance of NMDA receptor

hypofunction and thus the procognitive potential of enhancing

NMDA receptor signalling over the time course of disease

progression need to be much more clearly defined. Finally,

the relatively short treatment duration used in some clinical

trials, typically between 4 and 24 weeks (Choi et al., 2013)

with one study at amore lengthy 36 weeks (Iwata et al., 2015;

Table 3) may also contribute to the overall negative findings.

The role of AMPA receptors in cognition

AMPA receptors are heterotetramers formed from distinct

subunits (GluA1–4) or as Ca2+-permeable homotetramers

composed of GluA1 subunits (for review, see Henley and

Wilkinson, 2016). AMPA receptor expression and trafficking

is a highly dynamic process, regulated by neuronal activity,

and plays a central role in neuronal plasticity. PAMs of AMPA

receptors typically potentiate the channel-open state of the

receptor upon glutamate activation, enhance LTP and have

varying effects on long-term depression (LTD), depending

on the class of compound (Arai and Kessler, 2007). Promising

results from early studies reported that PAMs improve cognitive

function in human participants and in rodents. For example,

administration of the AMPA receptor PAM CX516

improved associative and recognition memory performance

in HCs (Ingvar et al., 1997). AMPA receptor PAMs have also

been reported to improve cognitive performance in ageing

healthy participants, in measures such as delayed recall performance

(Lynch et al., 1997) and working memory

(Wezenberg et al., 2007). These findings are corroborated in

rodent studies, where administration of a benzamide AMPA

receptor PAM improved performance in discriminative and

spatial memory tasks in rats (Staubli et al., 1994). Rodent research

has also shown the drug reverses cognitive deficits in

subchronic PCP rodent models, relevant to SZ, in behaviours

such as attentional set-shifting (Broberg et al., 2009) and

novel object recognition (Damgaard et al., 2010). However,

CX516 was shown to be ineffective in improving deficits in

cognitive flexibility and working memory seen in patients

with SZ, when given as an adjuvant with antipsychotic drugs

(Goff et al., 2008). Therefore, the therapeutic potential of

AMPA receptor PAMs in SZ requires further investigation.

The role of metabotropic glutamate

receptor subtypes 2 and 3 (mGlu2 and

mGlu3) in cognition

Numerous studies have demonstrated the efficacy of mGlu2/3

agonists and PAMs in reversing cognitive dysfunction in

animal models. For example, mGlu2/3 agonists improve

acute PCP-induced working memory deficits (Eglumetad;

Moghaddam and Adams, 1998), and deficits in working

memory and latent inhibition in GluN1 knockout mice

(SAR218645; Griebel et al., 2016), and novel object recognition

performance in a post-weaning social isolation rat model

(LY379268; Jones et al., 2011). In addition, the mGlu2-selective

PAM was shown to improve cognitive flexibility in control

rats (Nikiforuk et al., 2010). However, some studies have

failed to reproduce these findings and also show that

mGlu2/3 agonists may actually worsen some aspects of cognition,

including working memory, when given alone

(Eglumetad in rodents and marmosets; Schlumberger

et al., 2009; Spinelli et al., 2005) or have no significant effect

in control animals (LY395756; Li et al., 2015). Therefore,

these compounds may only be effective in improving cognition

in states of glutamatergic dysfunction.

In human studies, mGlu2/3 receptor agonists have provided

some promising results, improving cognitive performance.

For example, LY2140023 demonstrated encouraging

results as a treatment for the positive and negative symptoms

in patients with SZ (Patil et al., 2007), but ultimately, the drug

failed to pass Phase III clinical trials (Adams et al., 2014). Unfortunately,

the procognitive effects of this drug were not

assessed in patients with SZ, and the putative procognitive effects

of mGlu2/3 PAMs in SZ are yet to be firmly established.

The role of themGlu5 receptor in

cognition

In disorders thought to involve NMDA receptor

hypofunction, such as SZ, drugs active at mGlu5 receptors

have been proposed as potential therapeutics, due to the

close functional coupling between the two receptors and

the ability of mGlu5 activation to potentiate NMDA receptor

activity (Awad et al., 2000; Pisani et al., 2001). A key focus of

research has been on PAMs of themGlu5 receptor, drugs that

act by binding to an allosteric site on the receptor to potentiate

its activation by glutamate (CPPHA; Chen et al., 2008;

CDPPB; Uslaner et al., 2009). In unimpaired (control) rodents,

mGlu5 PAMs have been shown to improve object recognition

memory (ADX47273; Liu et al., 2008a; CDPPB;

Uslaner et al., 2009), spatial learning (CDPPB and

ADX47273; Ayala et al., 2009), contextual fear acquisition

(DFPE; Gregory et al., 2013) and extinction learning (CDPPB;

Cleva and Olive, 2011). In rodents, mGlu5 PAMs have also

been shown to limit the impact of NMDA receptor antagonists

on cognition. For example, CDPPB reverses the

dizocilpine-induced deficits in NOR (Uslaner et al., 2009)

and cognitive flexibility, assessed using the ASST (Darrah

et al., 2008; LaCrosse et al., 2015). The mGlu5 PAM

ADX47273 has also been shown to decrease premature

responding in the 5-CSRTT test of impulsivity in traitimpulsive

rats and attenuates the increased impulsiveness in

rats following dizocilpine administration (Isherwood et al.,

2015). These procognitive effects are thought to bemediated

by the ability of mGlu5 PAMS to enhance synaptic plasticity,

through both the enhancement of LTP and LTD (Ayala

et al., 2009; Xu et al., 2013). However, while some of these effects

may be dependent on the interaction of the mGlu5 receptor

with the NMDA receptor, others may be independent

of this interaction (Rook et al., 2015).

There is also evidence of cognitive improvement with

negative allosteric modulation (NAM) of mGlu5 receptors.

For example, CTEP reverses an inhibitory avoidance deficit

in mice with 16p11.2 microdeletion (Tian et al., 2015).

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However, injection of the mGlu5 antagonist MPEP into the

lateral ventricles of control rats prior to training impairs

working memory performance in the radial arm maze

(Manahan-Vaughan and Braunewell, 2005) and systemic pretreatment

exacerbates dizocilpine-induced deficits in spatial

workingmemory (Homayoun et al., 2004). The mGlu5 NAMs,

basimglurant and MTEP, also impair performance in the

5-CSRTT in control animals (Isherwood et al., 2015). Overall,

these data suggest that an optimal level of mGlu5 activity is

required for effective cognition, and the preclinical research

suggests that mGlu5 receptors may be a promising therapeutic

target to improve cognitive deficits, at least in some disorders.

However, research in human subjects has yet to

demonstrate an effect of mGlu5-selective drugs on cognition

(Berry-Kravis et al., 2016).

Glutamatergic regulation of functional

brain network connectivity: insights

from pharmacological studies targeting

the NMDA receptor

The study of how drugs that target the glutamate system alter

functional brain network connectivity to influence cognition

is in its extreme infancy. However, recent data fromstudies characterizing

the impact of NMDA receptor antagonists on brain

network connectivity have provided new insight into the glutamatergic

regulation of brain connectivity. In addition, these

studies have highlighted the potential translational value of

the analysis of brain network connectivity, with the reported effects

appearing to be conserved between species (rodents, primates

and humans) and across imaging modalities, in

measures of brain network connectivity. Here, we provide a

brief overview of the studies that have characterized the impact

of NMDA receptor antagonists on functional brain network

connectivity. The results highlight the potential future

utility of this approach in studying other manipulations of

the glutamatergic system, whether they are pharmacological

or genetic, that are known to affect cognition.

Insights from rodent studies

characterizing the impact of NMDA

receptor antagonists on functional

brain network connectivity

Acute treatment with a subanaesthetic dose of ketamine

induces abnormal increases in functional brain network

connectivity as analysed using [14C]-2-deoxyglucose functional

brain imaging (Dawson et al., 2014). Ketamine

treatment increases the number of functional connections

and alters the topographic properties of functional brain

networks to increase clustering between local brain regions.

This suggests that subanaesthetic ketamine treatment affects

cognition by promoting abnormally enhanced functional

connectivity (FC) in local subsystems. From a neural subsystems

perspective, this includes abnormally increased local

FC between subfields of the PFC (Dawson et al., 2013), which

parallels the PFC regional hyperconnectivity induced by

subaneasthetic ketamine treatment in primates (Gopinath

et al., 2016) as well as during resting-state in humans

(Anticevic et al., 2015). In contrast, subanaesthetic ketamine

treatment in rats impairs long-range connectivity, including,

for example, decreased PFC FC to thalamic inputs (Dawson

et al., 2013; 2014). This suggests that ketamine treatment

both compromises the ability of the PFC to receive information

from other neural subsystems and that enhanced local

clustering within the PFC compromises the appropriate segregation

of the information received at the local level. These

two mechanisms may contribute to the impact of ketamine

on PFC-dependent cognitive processes in rodents (Nikiforuk

and Popik, 2014; Nikiforuk et al., 2016). In addition, FC between

neuromodulatory subsystems such as the dorsal raphe

nucleus, the origin of serotonergic (5-HT) innervation and

the locus coeruleus (LC) and the origin of noradrenergic

(NA) innervation to the PFC are abnormally enhanced by

acute NMDA receptor blockade (Dawson et al., 2013, 2014).

Both 5-HT and NA are known to modulate PFC-dependent

cognitive processes (Berridge and Spencer, 2016; Clarke

et al., 2007). Thus, the modification of the connectivity between

neuromodulatory subsystems and the PFC may be a

key mechanism contributing to the impact of acute NMDA

receptor blockade on cognition, in addition to the local

effects of ketamine in the PFC and other cognitive neural subsystems

(e.g. hippocampus). The disruption of thalamocortical

connectivity is a major effect of acute NMDA receptor

antagonist treatment, with the thalamic reticular nucleus being

a particularly important target (for review, see Pratt and

Morris, 2015). Interestingly, disrupted thalamocortical connectivity

is found both in rodents treated with ketamine,

when brain networks are analysed using [14C]-2-

deoxyglucose, and in human participants treated with

ketamine when analysed using resting-state magnetoencephalography

(Rivolta et al., 2015), supporting not only the conservation

of alterations in FC across species but also across

different imaging modalities. This conservation may be key

to facilitating translation in the context of identifying

procognitive drugs that target the glutamatergic system.

In contrast to the effects of acute NMDA receptor blockade,

prolonged NMDA receptor hypofunction, as induced

by subchronic PCP treatment, disturbs functional brain network

connectivity in rodents (Dawson et al., 2012; 2014). At

the global network scale, this results from a decreased number

of functional connections in the brain network, decreased

clustering and an increase in the number of functional connections

that must be traversed to reach one brain region

from another (a measure known as average pathlength,

Dawson et al., 2014). These global alterations strongly parallel

those reported in functional resting-state brain networks

of EST (Micheloyannis et al., 2006; Liu et al., 2008b),

supporting the translational potential of these network analyses.

Subchronic PCP treatment also results in decreased thalamic,

hippocampal and PFC connectivity and induces a

decrease in the functional integration between the hippocampus

and PFC (Dawson et al., 2012), which could contribute

to the cognitive deficits seen as a result of prolonged

NMDA receptor hypofunction. Decreased hippocampal-PFC

resting-state FC is also seen in patients with SZ (Kraguljac

et al., 2017) and genetic rodent models relevant to the disorder

(Dawson et al., 2015; Sigurdsson et al., 2010). Again, a

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central role for altered neuromodulatory systemconnectivity

is indicated as a result of prolonged NMDA receptor

hypofunction, with decreased PFC – LC connectivity supported

(Dawson et al., 2012).

Insights from human studies

characterizing brain network

connectivity alterations induced by

NMDA receptor antagonists

Graph theory approaches to characterizing altered brain network

connectivity have been widely applied in relation to

brain network connectivity in SZ patients (Micheloyannis

et al., 2006; Liu et al., 2008a; van den Heuvel et al., 2010; Hadley

et al., 2016) and in a range of other cognitive brain disorders.

However, very few studies have applied graph theory

network analysis in the context of pharmacologicallyinduced

NDMA receptor hypofunction in HCs. For example,

using task-free pharmacological MRI, Joules et al. (2015) report

increased degree centrality, indicative of the number of

functional connections that a given region has in the context

of the brain network, for the basal ganglia and decreased centrality

for cortical regions, including regions in the frontal

cortex, following ketamine administration (Joules et al.,

2015). No other graph theory measures were reported as a

part of this study, and the authors themselves highlight the

additional insight that the application of these additional

measures could give. The data-driven approach taken in this

study highlights the value of using graph theory approaches

to define alterations in network connectivity. The reduced

PFC connectivity induced by ketamine administration in this

study contrasts with the increased PFC connectivity reported

using FC analysis in HCs by others (Anticevic et al., 2015) and

the preclinical data that support the general enhancement of

PFC connectivity following ketamine administration

(Dawson et al., 2014). The reasons for this disparity remain

unclear but may include the use of only one form of connectivity

analysis in the study of Joules et al. (2015) (degree centrality)

or that the regions of interest that were included in

the analysis influenced the findings (as ketamine treatment

has been shown to increase and decrease PFC connectivity

to different brain regions; Dawson et al., 2013). For example,

another recent study used a seed regional approach to characterizing

the impact of ketamine on PFC-hippocampal connectivity

in HCs, which indicates a ketamine-induced

increase in the FC between these neural subsystems (Grimm

et al., 2015). Interestingly, this investigation also confirmed

similar effects in rodents using the same approach, further

highlighting the translational value of measuring functional

brain network connectivity.

As the application of graph theory methods in the context

of NMDA receptor antagonist-induced alterations in brain

network FC is relatively limited, here, we also consider the effects

on task-based FC from fMRI studies. To date, the vast

majority of these studies have been applied in the context

of the influence of NMDA receptor antagonists during working

memory tasks, which has potential translational confounds

when attempting to compare the observed effects

with those seen in resting-state brain imaging data. However,

overall, the effects reported seem to be similar to those found

when brain imaging is undertaken at rest, and in animal

models. For example, Driesen et al. (2013) found that acute

ketamine administration significantly reduced FC between

the DLPFC and middle frontal gyrus and impaired performance

during working memory function in HCs. In a more

recent study, dextromethophan led to increased FC within a

brain network comprising 270 seed regions involving the

DLPFC (Braun et al., 2016). The findings parallel the increased

DLPFC FC seen during working memory function in patients

with SZ (Siebenhuhner et al., 2013). Anticevic et al. (2012)

also found that ketamine administration increased task-based

FC in the fronto-parietal network and reduced taskdeactivated

FC of the defaultmode network during a working

memory task (Anticevic et al., 2012), which also appears to be

similar to the effects seen in patients with SZ. To date, only

these three studies have reported the effects of NMDA receptor

antagonists on alterations in task-based FC in HCs. More

research into the impact of NMDA receptor antagonists, and

other glutamatergic compounds, on working memory and

brain network connectivity is needed in order to gain a better

understanding of the effects of glutamatergic modulators on

cognitive function and their role in SZ. Multi-modal studies

of cognitive function, with the simultaneous measurement

of glutamatergic concentrations (using magnetic resonance

spectroscopy) in combination with BOLD fMRI, may lead to

greater insights into glutamatergic responses during cognitive

functions in patients with SZ (for example, see Taylor

et al., 2015).

Conclusion

The glutamatergic system plays a primary role in the regulation

of multiple domains of cognition. Targeting glutamatergic

neurotransmission offers hope for the treatment of

cognitive deficits seen in patients with SZ and other brain disorders

with pronounced cognitive deficits. Characterizing

the effect of a modified glutamate system function on brain

network connectivity offers new systems-level insight into

the mechanisms underlying the glutamatergic regulation of

cognition. The study of how functional brain networks are

modulated by glutamateric neurotransmission is in its extreme

infancy. Here, we have outlined recent studies that

have characterized the impact of NMDA receptor antagonists

on brain network connectivity as a leading exemplar of the

new insight that can be gained fromthe study of how the glutamate

system modulates brain network connectivity and

cognition. The use of this approach may provide results that

have great translational value, as initial observations appear

to be conserved across different species and imaging modalities.

Future studies dedicated to investigating the effects of

other procognitive compounds and modifications of glutamatergic

system function, whether they are pharmacological

or genetic, should be undertaken in order to further understand

the mechanisms through which these manipulations

elicit their effects on cognition.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are

hyperlinked to corresponding entries in http://www.

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guidetopharmacology.org, the common portal for data from

the IUPHAR/BPS Guide to PHARMACOLOGY (Southan

et al., 2016), and are permanently archived in the Concise

Guide to PHARMACOLOGY 2015/16 (Alexander et al.,

2015a,b).

Conflict of interest

The authors declare no conflicts of interest.

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