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The influence of the glutamatergic system on cognition in schizophrenia: A systematic review

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ABSTRACT

Previous literature showing the role of the glutamatergic system on cognition in schizophrenia has been inconclusive. 44 relevant pharmacological, candidate gene and neuroimaging studies were identified through systematic search following PRISMA guidelines. To be included, studies must have observed at least one objective measure of cognitive performance in patients with schizophrenia and either manipulated or measured the glutamatergic system. Of the cognitive domains observed, memory, working memory and executive functions appear to be most influenced by the glutamatergic pathway. In addition, evidence from the literature suggests that presynaptic components synthesis and uptake of glutamate is involved in memory, while postsynaptic signalling appears to be involved in working memory. In addition, it appears that the glutamatergic pathway is particularly involved in cognitive flexibility and learning potential in regards to executive functioning. The glutamatergic system appears to contribute to the cognitive deficits in schizophrenia, whereby different parts of the pathway are associated with different cognitive domains. This review demonstrates the necessity for cognition to be examined by domain as opposed to globally.

1. Introduction

Schizophrenia is a debilitating mental disorder prevalent in 1% of the population, with symptoms often categorised into three groups; positive, negative and cognitive. Antipsychotic medications are designed to target the positive symptoms; however, negative and cognitive symptoms respond poorly (Buchanan et al., 1998). Cognitive problems, such as deficits in areas of executive functioning, including working memory and inhibition, as well as memory and attention, are a core feature of schizophrenia (Kiehl et al., 2000; Minzenberg et al., 2009; Weickert et al., 2000). Cognitive problems relate to a poorer quality of life. Better targeted cognitive treatments would allow affected individuals to function better in society. Interventions such as psychological therapies, community treatment, skills training, cognitive remediation and supported employment are currently available for individuals with schizophrenia, although studies have shown that this has a limited effect on improving quality of life, social or cognitive functioning (Pilling et al., 2002). Patients with schizophrenia have been estimated to be one to two standard deviations below the scores of healthy controls in terms of cognitive function (Nielsen, 2011), and cognitive symptoms are present at a higher level in unaffected biological relatives compared to the general population, indicating a genetic contribution to the cognitive impairment. Schizophrenia has been shown to be largely influenced by genetic factors, with a heritability of 70–85% (Lewis et al., 2003). As such, a key focus in recent literature has been to look at potential genetic pathways to gain a better understanding of the molecular mechanisms behind cognitive dysfunction in schizophrenia.

One potential molecular mechanisms influencing cognition in schizophrenia is related to the glutamate metabolism pathway, known as the 'glutamate hypothesis' (Jia et al., 2010). Glutamate is a primary excitatory neurotransmitter and is controlled by N-methyl-D-aspartate (NMDA) receptors. These NMDA receptors control synaptic plasticity and memory function, and NMDA antagonists have the ability to mimic cognitive impairment and negative symptoms of schizophrenia (Coyle and Tsai, 2004; Neill et al., 2010). The 'glutamate hypothesis,' evolved from studies involving NMDA receptor antagonists Phencyclidine (PCP) and ketamine administered to healthy participants. Studies have shown that PCP or ketamine mimic both positive and negative symptoms of schizophrenia (Adler et al., 2014; Allen and Young, 1978). Ketamine has also been shown to induce brief psychosis in healthy controls (Malhotra et al., 1996). As both ketamine and PCP have been shown to

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Table 1
Summary of pharmacological studies investigating the influence of the glutamatergic system on cognition in schizophrenia.

Reference	Drug	Study design	Patients	Cognitive task(s)[a]	Cognitive Domain[b,c]								Significant results[b,d] (in patients unless otherwise stated)	Effect size	Standardized effect size (Cohen's d)
					M	WM	EF	VF	A	I	PS	SoP			
Buchanan et al. (2007)	D-cycloserine	16 week double blind placebo controlled RCT; adjunctive glycine, D-cycloserine, or placebo	157	WAIS Digit symbol, WAIS symbol search, CFT, Phonemic verbal fluency, Grooved peg Board, CPT, Rey AVLT, BVMT, LNS, Spatial Working Memory Delay, WCST	–	–	–	–			–	–			
Chengappa et al. (2012)	L-carnosine	3 month double blind, placebo RCT; adjunctive	75	Strategic Target Detection Test, Set Shifting, Auditory DS, FT, Word-List Memory, Working Memory test	–		↑		–		–		Set shifting task: Basal reaction time State imitation reaction time End imitation reaction time Strategic target detection test: Strategic efficiency Perseverative errors	 Partial η^2 = 0.052 Partial η^2 = 0.07 Partial η^2 = 0.07 d = 0.30 V = 0.035	 0.47 0.55 0.55 0.30 N/A
Evins et al. (2002)	D-cycloserine	Four month stable dose of risperidone, followed by two week trials of placebo and four doses of d-cycloserine; adjunctive	10	Word-List Memory, FT, DS, Stroop			–		–	–	–				
Goff et al. (1995)	D-cycloserine	Four month stable dose of conventional neuroleptics , followed by two week trials of placebo and four doses of d-cycloserine; adjunctive	9	SIRP		↑							SIRP mean reaction time	N/A	N/A
Goff et al. (1999)	D-cycloserine	8 week double blind, placebo controlled RCT; adjunctive	39	SIRP, Stroop, the Miller-Selfridge Test, VFT, DS, FT		–			–	–	–				
Goff et al. (2008)	CX516 (Ampakine)	4 week double blind, placebo controlled RCT; adjunctive	95	North American Adult Reading Test, TMT, Degraded-stimulus CPT, California Verbal Learning Test, Faces and Family Pictures subtests (WMS-III), WCST, LNS, Grooved Peg Board, Letter and CFT	–		–		–		–	–			
Kelly et al. (2015)	Minocycline	10 week double blind, placebo controlled RCT; adjunctive minocycline or placebo added to clozapine	52	MATRICS	–	↑	–	–	–			–	Working memory composite score	d = 0.41	0.41
LaPorte et al. (1996)	Ketamine	Double blind cross-over study; ketamine injections or placebo; adjunctive	7	COWA, CFT, line bisection, serial digit learning, logical memory, figural reproduction	–			–	–						
Levkovitz et al. (2010)	Minocycline	6 month double blind, placebo-controlled, RCT; ; adjunctive; 54 patients randomly allocated in a 2:1 ratio to minocycline	70	CANTAB	↑	↑	↑		–		–		Time x treatment interaction: Spatial Recognition Memory (M) Spatial WM errors (WM) Executive functioning composite score (EF) ID/ED post-extradimensional errors (EF) ID/ED stages completed (EF) Stockings of Cambridge problems solved (EF)	r = 0.61 r = 0.58 r = 0.47 r = 0.42 r = 0.31 r = 0.36	1.54 1.42 1.07 0.93 0.65 0.77
Lieberman et al.	Memantine	8 week double blind, placebo	138	BACS	–	–	–	–	–		–	–			

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