Neuroscience and Biobehavioral Reviews 72 (2017) 50–67

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

A review of molecular genetic studies of neurocognitive deficits in schizophrenia

Gwyneth Zai[a,b,c,d,*], Trevor W. Robbins[c,e], Barbara J. Sahakian[c,d], James L. Kennedy[a,b]

[a] Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Canada
[b] Department of Psychiatry and Institute of Medical Science, University of Toronto, Toronto, Canada
[c] MRC/Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK
[d] Department of Psychiatry, University of Cambridge, Cambridge, UK
[e] Department of Psychology, University of Cambridge, Cambridge, UK

ARTICLE INFO

Article history:
Received 1 December 2015
Received in revised form 17 October 2016
Accepted 27 October 2016
Available online 17 November 2016

Keywords:
Genetics
Schizophrenia
Neurocognition
Cognitive deficits
Candidate gene studies
Genome-wide association studies (GWASs)

ABSTRACT

Schizophrenia is a complex and debilitating illness with strong genetic loading. In line with its heterogeneous symptomatology, evidence suggests genetic etiologies for the phenotypes in schizophrenia. A search across endophenotypes has pointed towards consistent findings in its neurocognitive deficits. Extensive literature has demonstrated impaired cognition including executive function, attention, and memory in schizophrenia patients when compared to healthy subjects. This review (1) provides an overview of recent studies and (2) develops an up-to-date conceptualization of genetic variations influencing neurocognitive functions in schizophrenia patients. Several neurotransmitter system genes have been examined given knowledge of their role in brain functions and their reported genetic associations with schizophrenia and cognition. Several genetic variations have emerged as having preliminary effects on neurocognitive deficits in schizophrenia. These include genes in the neurotrophic, serotonin, cell adhesion, and sodium channel systems. Limited evidence also suggests the dopaminergic system genes, with the most studied catechol-o-methytransferase (*COMT*) gene showing inconsistent findings. Further investigations with larger samples and replications are required to elucidate genetic risk for cognitive deficits in schizophrenia.

Contents

1. Introduction

Schizophrenia is a chronic and severe neuropsychiatric disorder with a lifetime prevalence of 0.4–1% in the general population (APA,

* Corresponding author at: Centre for Addiction and Mental Health, 250 College Street, Toronto, ON M5T 1R8, Canada.
E-mail address: gwyneth.zai@camh.ca (G. Zai).

http://dx.doi.org/10.1016/j.neubiorev.2016.10.024
0149-7634/

2013; McGrath et al., 2008). The core features of this disorder are characterized by three symptom domains including positive symptoms, negative symptoms, and cognitive deficits (APA, 2013). The identification of neurocognitive deficits in schizophrenia patients is important because cognitive impairment is associated with poor functional outcome (Lepage et al., 2014). Up to 98% of schizophrenia patients have a degree of neurocognitive impairment (Heinrichs and Zakzanis, 1998; Keefe et al., 2005). Although antipsychotic medications reduce positive symptoms significantly, they have limited efficacy for remediating neurocognitive deficits and negative symptoms of schizophrenia (Carpenter and Koenig, 2008; Keefe and Harvey, 2012).

Cognitive dysfunction has repeatedly been identified as one of the hallmark features of schizophrenia starting as early as 1950 by Bleuler (1950) and recently in the past decade (Lepage et al., 2014; Heinrichs and Zakzanis, 1998; Green et al., 2000; Barnett et al., 2010). A systematic review reported global cognitive impairment and specifically worse verbal memory, executive function, and general IQ, in first-episode psychotic patients when compared to healthy controls (Aas et al., 2014). Recent meta-analyses also detected significant deficits in working memory, attention/vigilance, verbal/visual learning and memory, executive functions (reasoning and problem solving), processing speed, social cognition, and psychomotor control (Keefe and Harvey, 2012; Green et al., 2004).

Evidence has shown that schizophrenia and cognitive impairment have heritability ranging between 70 and 90% and 24 and 55% respectively (Greenwood et al., 2007; Sabb et al., 2008). Schizophrenia is a complex and heterogeneous neuropsychiatric disorder with a polygenic architecture (Sullivan et al., 2012) and even following recent genome-wide association studies (GWAS) (Ripke et al., 2013; Biological insights, 2014), multiple small gene effects with only several replicable findings have been found to contribute to risk. Therefore, the identification of endophenotypes, with an attempt to ascertain a more homogeneous phenotype for genetic studies, is important for elucidating the etiology of schizophrenia. The search for endophenotypes is guided by their strong association with the illness, high heritability, and observable similar deficits in unaffected relatives (Gur et al., 2007). Cognitive deficits are heritable and are core features of schizophrenia, thus they may be valuable endophenotypes for schizophrenia. Twin studies (Cannon et al., 2000; Pardo et al., 2000; Toulopoulou et al., 2007) and two recent molecular genetic studies (Lencz et al., 2014; Fernandes et al., 2013) have reported significant genetic overlap between neurocognition and schizophrenia. Additionally, neuropsychological studies have observed that unaffected relatives of schizophrenia patients performed significantly worse in estimated intelligence, immediate and delayed logical memory, immediate visual reproduction, and sustained attention, therefore implicating genetic loading within families (Faraone et al., 2000; Agnew-Blais and Seidman, 2013; Hilti et al., 2010). Although research on the genetics of neurocognitive domains in schizophrenia has grown rapidly over the last decade in parallel with attempts to determine the genetic etiology of schizophrenia, the last review to have covered some genetic studies of cognitive endophenotypes in schizophrenia was published in 2008 (Golimbet, 2008). Therefore, we now provide an up-to-date review of this important topic.

1.1. Methods

We reviewed all molecular genetic studies of cognition in schizophrenia that were published in PubMed and/or MEDLINE until January 1, 2015. Specific search terms used included: genetics, molecular genetics, schizophrenia, cognition, neurocognition, cognitive or neurocognitive or neuropsychological deficits or impairments or endophenotypes or traits. Eighty-two original studies were included in this review article. A summary can be found on Table 1

(Table S1 in Supplement 1 for full details).

1.2. Results

Many genes have been reported to be associated with cognitive impairment in schizophrenia as shown in Table S1 in Supplement 1. The next sections of this review will provide a comprehensive summary of these genetic findings organized according to important bio-molecular systems (Fig. 1).

1.2.1. Dopaminergic system genes

The dopaminergic system genes that have been investigated in neurocognitive deficits of schizophrenia include catechol-*O*-methyltransferase (*COMT*) (Barnett et al., 2010, 2007; Nicodemus et al., 2013; Cruz et al., 2013; Alfimova et al., 2006, 2013; Bilder et al., 2002; Bosia et al., 2007; Egan et al., 2001; Galderisi et al., 2005a; Goldberg et al., 2003; Golimbet et al., 2006; Joober et al., 2002; Nolan et al., 2004; Rosa et al., 2004; Rybakowski et al., 2006a; Szoke et al., 2006; Greenwood et al., 2011; Cassidy et al., 2014; Swaminathan et al., 2012; Ayoub et al., 2012), dopamine transporter (*DAT*) (Barnett et al., 2010; Nicodemus et al., 2013; Rybakowski et al., 2006a; Ayoub et al., 2012; Szekeres et al., 2004), dopamine D1 receptor (*DRD1*) (Barnett et al., 2010), dopamine D2 receptor (*DRD2*) (Barnett et al., 2010; Alfimova et al., 2013; Cassidy et al., 2014), dopamine D3 receptor (*DRD3*) (Barnett et al., 2010; Swaminathan et al., 2012; Szekeres et al., 2004), dopamine D4 receptor (*DRD4*) (Alfimova et al., 2006), dopamine D5 receptor (*DRD5*) (Golimbet et al., 2008), dopamine beta-hydroxylase (*DBH*) (Green et al., 2004; Swaminathan et al., 2012), vesicular monoamine transporter 2 (*SLC18A2*) (Barnett et al., 2010; Swaminathan et al., 2012), ankyrin repeat and kinase domain containing 1 (*ANKK1*) (Barnett et al., 2010), and protein phosphatase 1, regulatory (inhibitor) subunit 1B (*PPP1R1B*) (Barnett et al., 2010).

The most extensively examined candidate gene in neurocognition of schizophrenia is *COMT*. A reduction in dopaminergic neurotransmission in specific brain regions such as the anterior cingulated and the dorso-lateral prefrontal cortex has been postulated to alter cognition, specifically executive function and working memory, in schizophrenia (Malhotra et al., 2002). A functional polymorphism within *COMT*, Val158Met, accounts for a four-fold variation in its enzymatic activity and dopamine catabolism in the prefrontal cortex, with Met as the low functioning allele (Egan et al., 2001). Twenty three studies were found as defined by our search criteria (Barnett et al., 2007). Barnett et al. (2007) performed a meta-analysis including 12 studies of the impact of *COMT* Val158Met on executive function and detected significant association between Val/Val and worse cognitive performance than Met/Met only in healthy controls but not in schizophrenia patients. A recent study (Alfimova et al., 2013) similarly reported no association between this locus and theory of mind dysfunction in schizophrenia but detected worse performance in Met-carrier females in the combined schizophrenia and control sample. However, a 94-multi-gene family study examining *COMT*, found associations with verbal learning, 'false' memory, and prepulse inhibition in schizophrenia patients (Greenwood et al., 2011). Twamley et al. (2014) also reported better learning, memory, and abstraction with the Met allele than Val, and when Green et al. (2014) investigated cognitive function in schizophrenia patients with childhood trauma history, they detected significant links of the Val homozygotes with worse cognitive performance in the absence of childhood adversity, and better executive function with positive abuse history, suggesting a gene-environment interaction. Overall, given the pleiotropic effects of most genes, it appears unlikely that