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Review

The muscarinic system, cognition and schizophrenia

Sean P. Carruthers [a,b,*], Caroline T. Gurvich [b], Susan L. Rossell [a,b,c]

[a] Brain, Psychological Sciences Research Centre (BPsyC), Faculty of Health, Arts, Design, Swinburne University of Technology, Melbourne 3122, VIC, Australia
[b] Monash Alfred Psychiatry Research Centre (MAPrc), Monash University Central Clinical School and The Alfred Hospital, Melbourne 3004, VIC, Australia
[c] Psychiatry, St Vincent's Hospital, Melbourne 3065, VIC, Australia

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ABSTRACT

An increasing body of evidence has implicated the central muscarinic system as contributing to a number of symptoms of schizophrenia and serving as a potential target for pharmaceutical interventions. A theoretical review is presented that focuses on the central muscarinic system's contribution to the cognitive symptoms of schizophrenia. The aim is to bridge the void between pertinent neuropsychological and neurobiological research to provide an explanatory account of the role that the central muscarinic system plays in the symptoms of schizophrenia. First, there will be a brief overview of the relevant neuropsychological schizophrenia literature, followed by a concise introduction to the central muscarinic system. Subsequently, we will draw from animal, neuropsychological and pharmacological literature, and discuss the findings in relation to cognition, schizophrenia and the muscarinic system. Whilst unifying the multiple domains of research into a concise review will act as a useful line of enquiry into the central muscarinic systems contribution to the symptoms of schizophrenia, it will be made apparent that more research is needed in this field.

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Schizophrenia is a debilitating psychiatric illness that significantly impedes on normal vocational and social functioning (Mueser and McGurk, 2004; van Os and Kapur, 2009). Characterized by a constellation of signs and symptoms, schizophrenia is a heterogeneous clinical syndrome, with no single symptom being pathognmonic of the disorder. Despite it being almost 100 years since Kraepelin's (1919) seminal description of dementia praecox, effective management of all of the symptoms of schizophrenia remains elusive. Whilst current antipsychotic medications provide modest management of the positive/psychotic symptoms of schizophrenia for the majority of patients, such medications fail to adequately address the negative and cognitive symptoms prevalent in the disorder (Minzenberg and Carter, 2012; Swartz et al., 2008). Furthermore, current treatment regimes are marred by

* Corresponding author at: Swinburne University of Technology, Faculty of Health, Arts, Design, John Street, Hawthorn, 3122 Melbourne, VIC, Australia. Tel.: +61 3 9214 5553.
E-mail address: scarruthers@swin.edu.au (S.P. Carruthers).

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dose-limiting side-effects and patient non-compliance (Miyamoto et al., 2005; Sendt et al., 2015), highlighting the need for more effective and tolerable treatment options.

Increasing investigative interest has been directed towards uncovering the underlying causes of the cognitive symptoms of schizophrenia and the development of novel drugs aimed at alleviating the burden of these symptoms (e.g. Davie et al., 2013; Foster et al., 2014; Ibrahim and Tamminga, 2012). Promising research points to an abnormal central muscarinic system as a likely facilitator of cognitive dysfunction amongst schizophrenia patients, whilst also contributing to some of the positive/psychotic symptoms prevalent in the disorder. The following review will summate the relevant basic and clinical research findings associated with the muscarinic system and schizophrenia, in addition to providing a concise account of the growing pharmacological literature associated with the development of drugs that target this system.

1. Schizophrenia: A cognitive overview

In addition to the combinations of positive and negative symptoms, almost all patients with schizophrenia experience some form of cognitive impairment. Patients with the disorder typically perform one to two standard deviations below healthy controls on a range of neurocognitive measures, with the most prominent impairments seen in learning and memory, working memory, attention, problem solving, processing speed and social cognition (Keefe and Fenton, 2007; Nuechterlein et al., 2004). Considered by some scholars to be the most persistent and characteristic features of the disorder (Daban et al., 2006; Green et al., 2004; Kahn and Keefe, 2013; Lewis, 2004; Tabarés-Seisdedos et al., 2008), the severity of cognitive impairment has been significantly linked to global functional outcome (Bowie et al., 2006; Green et al., 2004; Tabarés-Seisdedos et al., 2008), patient quality of life (Fiszdon et al., 2008; Savilla et al., 2008), success in psychosocial rehabilitation programs and employment retention (Bryson and Bell, 2003; Green et al., 2000).

Developmental deficits across various cognitive domains, such as working memory and executive functioning are prevalent in children who eventually go on to develop schizophrenia (Niemi et al., 2003; Reichenberg et al., 2010). Likewise, longitudinal studies examining symptom progression amongst high-risk adolescents depict a progressive decline in various cognitive domains, including verbal and working memory (Lencz et al., 2006; Simon et al., 2007), attention (Wood et al., 2008) and executive functioning (Kim et al., 2011; Üçok et al., 2013). Such progressive developmental or prodromal cognitive decline is not a feature of other psychiatric disorders such as bipolar (Lewandowski et al., 2011; Sørensen et al., 2012) and has been shown to precede the onset of psychosis by an average of nine years (Van Oel et al., 2002), causing some to argue that early cognitive decline is a hallmark feature of schizophrenia (see Kahn and Keefe, 2013).

Whilst current atypical antipsychotic medications can produce mild improvements in general cognition (Désaméricq et al., 2014; Woodward et al., 2005), longitudinal evidence indicates that this is only apparent within the first two months of treatment, after which the therapeutic effects stagnate (Keefe et al., 2007). Attempts are being made to develop novel nootropic drugs that can improve cognitive function amongst schizophrenia patients, however just as no single symptom is pathognomonic of schizophrenia, no single neurotransmitter system is responsible for causing the diverse range of cognitive symptoms (Ibrahim and Tamminga, 2011; Tamminga, 2006). Rather, individual systems contribute to various clusters of symptoms and thus contemporary schizophrenia research has focused on identifying and examining which neurotransmitter system contributes to what cognitive symptoms of the disorder (Abi-Dargham et al., 2002; Ibrahim and Tamminga, 2011, 2012). Multiple lines of evidence (see below) have implicated a dysfunctional central muscarinic system in the pathogenesis of the cognitive symptoms of schizophrenia, in addition to also contributing to some of the pervasive positive symptoms characteristic of the psychiatric disorder.

2. A quick overview of the muscarinic system

The muscarinic system represents one half of the cholinergic system, one of the most important neuromodulatory neurotransmitter systems in the brain. The central cholinergic system innervates a diverse range of cortical and subcortical structures, interacting with two structurally diverse families of receptors, the nicotinic and muscarinic receptors, through coordinated acetylcholine (ACh) release (Lucas-Meunier et al., 2003; Mesulam, 2004). Two major sub-constellations of cholinergic projections exist that construct the central cholinergic system and facilitate a diverse range of autonomic and higher cortical processes. First, the pedunculopontine cholinergic complex, which projects to various midbrain and brainstem structures (Iversen et al., 2009; Mesulam, 2004; Mesulam et al., 1983). Second, the basal forebrain complex, which originates in the nucleus basalis of meynert and projects to the hippocampus and a number of cortical regions including the frontal and dorsolateral prefrontal cortices (Henny and Jones, 2008; Mesulam, 2004; Mufson et al., 2003). It is through the basal forebrain complex that the cholinergic system is said to facilitate a range of cognitive processes via ACh's interaction with both the nicotinic and muscarinic receptors (see Eglen, 2006; Lucas-Meunier et al., 2003; Sarter et al., 2005).

Genes have been cloned for two families of nicotinic receptors that can be further differentiated into a total of 12 neuronal subunits. Whilst being critically involved in autonomic functioning, the nicotinic system has been implicated in contributing to various cognitive functions (e.g. Lendvai et al., 2013; Logue and Gould, 2014), the full extent to which has yet to be uncovered due to the system's structural complexity (for a comprehensive review of the nicotinic system, see Gotti and Clementi, 2004; Gotti et al., 2006). In contrast, the muscarinic system is comprised of only five receptor subtypes (M1-5) that either innervate or inhibit neural activity depending on the structure of the receptor and its location in reference to the synapse (Bonner et al., 1987; Kubo et al., 1986). Grouped together as the M1-like receptors, M1, M3 and M5 receptors are located post-synaptically and when innervated by ACh promote neural transmission. Conversely, the M2 and M4 receptors, referred to as M2-like receptors, are located at both the pre- and post-synaptic site and act as autoreceptors, a category of receptor that restricts ongoing synaptic activity by constraining the release or ongoing synthesis of a set neurotransmitter (see Zhang et al., 2002). When innervated, the M2-like receptors actively reduce or inhibit ACh mediated activity (for a comprehensive review of the molecular biology and biochemistry of the central muscarinic system, see Eglen, 2005, 2006; Lanzafame et al., 2003).

All five muscarinic receptors are expressed throughout the mammalian brain; however, the concentration of each receptor varies between regions. M1 and M2 receptors are highly expressed in all major forebrain areas, with the M1 receptor being the most abundant muscarinic receptor in the cortex, hippocampus and striatum, with high concentrations of the M2 receptor found in the nucleus basalis and occipital cortex (Flynn et al., 1995; Levey, 1993; Levey et al., 1991). M3 receptors are expressed with a similar cortical distribution to that of the M1 receptor, however in substantially lower concentrations (Levey et al., 1994); with M4 receptors more prominent within the striatum and caudate putamen and to a lesser degree in the cortex and hippocampus (Levey, 1993; Levey

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