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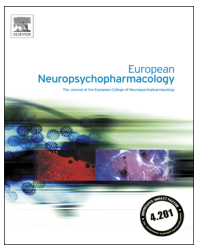

Negative symptoms of schizophrenia: Clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment

Mark J. Millan[a,*], Kevin Fone[b], Thomas Steckler[c], William P. Horan[d]

[a]*Pole of Innovation in Neuropsychiatry, Institut de Recherche Servier, 125 Chemin de Ronde, 78290 Croissy-sur-Seine, Paris, France*
[b]*School of Biomedical Sciences, Medical School, Queen's Medical Centre, Nottingham University, Nottingham NG72UH, UK*
[c]*Janssen Research and Development, Turnhoutseweg 30, 2340 Beerse, Belgium*
[d]*VA Greater Los Angeles Healthcare System, University of California, Los Angeles, MIRECC 210A, Bldg. 210, 11301 Wilshire Blvd., Los Angeles, CA 90073, USA*

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Abstract
Schizophrenia is a complex and multifactorial disorder generally diagnosed in young adults at the time of the first psychotic episode of delusions and hallucinations. These positive symptoms can be controlled in most patients by currently-available antipsychotics. Conversely, they are poorly effective against concomitant neurocognitive dysfunction, deficits in social cognition and negative symptoms (NS), which strongly contribute to poor functional outcome. The precise notion of NS has evolved over the past century, with recent studies – underpinned by novel rating methods – suggesting two major sub-domains: "decreased emotional expression", incorporating blunted affect and poverty of speech, and "avolition", which embraces amotivation, asociality and "anhedonia" (inability to *anticipate* pleasure). Recent studies implicate a dysfunction of frontocortico-temporal networks in the aetiology of NS, together with a

Abbreviations: BTBR, Black and Tan Brachyury; CB, Cannibinoid; CBT, Cognitive-Behavioural Therapy; CRT, Cognitive Remediation Therapy; DA, dopamine; DLPFC, Dorsolateral Prefrontal Cortex; DSM, Diagnostic and Statistical Manual; EEG, electroencephalography; ERP, Event Related Potential; fMRI, functional Magnetic Resonance Imaging; LSD, Lysergic-diethylamide; MHC, Major Histocompatability Complex; MRI, Magnetic Resonance Imaging; NIMH, National Institute of Mental Health; NMDA, N-Methyl-D-Aspartate; OFC, orbitofrontal cortex; PAM, positive Allosteric Modulator; PANSS, Positive and Negative Symptom Scale; PCP, Phencyclidine; NS, negative symptoms; PET, Positron Emission Tomography; PFC, prefrontal cortex; rTMS, repetitive Transcranial Magnetic Stimulation; SPECT, Single Photon Emission Computerised Tomography; USV, Ultrasonic Vocalisation; VHL, ventral hippocampus lesion

*Corresponding author. Tel.: +33 1 5572 2425; fax: +33 1 5572 2082.
E-mail address: mark.millan@fr.netgrs.com (M.J. Millan).

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disruption of cortico-striatal circuits, though other structures are also involved, like the insular and parietal cortices, amygdala and thalamus. At the cellular level, a disruption of GABAergic-glutamatergic balance, dopaminergic signalling and, possibly, oxytocinergic and cannibinoidergic transmission may be involved. Several agents are currently under clinical investigation for the potentially improved control of NS, including oxytocin itself, N-Methyl-D-Aspartate receptor modulators and minocycline. Further, magnetic-electrical "stimulation" strategies to recruit cortical circuits and "cognitive-behavioural-psychosocial" therapies likewise hold promise. To acquire novel insights into the causes and treatment of NS, experimental study is crucial, and opportunities are emerging for improved genetic, pharmacological and developmental modelling, together with more refined readouts related to deficits in reward, sociality and "expression". The present article comprises an integrative overview of the above issues as a platform for this Special Issue of European Neuropsychopharmacology in which five clinical and five preclinical articles treat individual themes in greater detail. This Volume provides, then, a framework for progress in the understanding – and ultimately control – of the debilitating NS of schizophrenia.
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1. Introduction

1.1. Schizophrenia: core characteristics and inadequate current management

Schizophrenia is a chronic, life-long and debilitating disorder which is triggered in a complex, heterogeneous and multifactorial fashion by a diverse palette of genetic, epigenetic, developmental and environmental risk factors (Figure 1) (Millan, 2013; Sullivan et al., 2012; Rapoport et al., 2012). It occurs with an incidence of at least 0.7% of the population and, quite apart from personal distress, schizophrenia has a huge socioeconomic burden, mostly in terms of indirect costs like loss of employment and social support (Wittchen et al., 2011). Diagnosis generally occurs in the young adult (or in late adolescence) with the advent of the first frank psychotic episode, often in the wake of a high-risk, prodromal period in which occasional and/or attenuated psychotic symptoms may occur – though such high risk individuals may eventually transit to another psychiatric disorder like depression (Fusar-Poli et al., 2013a, 2014; Sabbag et al., 2011).

Psychosis corresponds to the most familiar cluster of cardinal symptoms, termed positive, and including delusions and hallucinations (Buchanan et al., 2010; Huxley and Fonseca, 2014; Leucht et al., 2013; Tandon et al., 2013). Positive symptoms have long been treated by "first-generation" neuroleptics like haloperidol and chlorpromazine; by clozapine; and by a range of more recently-developed "second-generation" antipsychotics including risperidone, olanzapine and aripiprazole (Asenjo-Lobos et al., 2010; Citrome, 2013; Hartling et al., 2012; Leucht et al., 2009, 2013; Naber and Lambert, 2009). Nonetheless, control is often incomplete and some 20–30% of patients are considered refractory (not responsive to at least two different treatments). Despite decades of effort to find successor agents of improved efficacy, clozapine remains the most effective agent in otherwise non-responsive patients. However, as outlined below, clozapine shares the comparative inactivity of other classes of antipsychotic for the management of neurocognitive dysfunction, impaired social cognition and negative symptoms (NS) (Asenjo-Lobos et al., 2010; Leucht et al., 2009, 2013).

Deficits in multiple domains of "neurocognition" are marked, ranging from attention to working memory to executive function, and they are little improved by medication, though Cognitive Remediation Therapy (Section 4.7) is attracting interest as an alternative therapeutic approach (Buchanan et al., 2010; Carter and Barch, 2007; Kalkstein et al., 2010; Leucht et al., 2009, 2013; Millan et al., 2012; Naber and Lambert, 2009; Wykes et al., 2011). The poor response to antipsychotics is hardly surprising since blockade of dopamine D2 receptors, muscarinic M1 receptors, histamine H1 receptors and α1-adrenoceptors will compromise mnemonic performance and overwhelm any potentially beneficial influence on cognition, such as that afforded by antagonism of frontocortical D3 receptors or α2-adrenoceptors (Brosda et al., 2014; Citrome, 2013; Millan et al., 2000, 2012; Nakajima et al., 2013). This may at least partially explain why numerous mechanisms evaluated as "add-on" therapies to antipsychotics have disappointed for improving neurocognition (Buchanan et al., 2011a, 2011b; Millan et al., 2012).

A further domain of poorly-treated impairment in schizophrenia is social cognition which refers to mechanisms for understanding and interpreting the mental states, gestures, behaviours and facial expressions of others, and which also embraces the understanding of verbal and non-verbal modes of communication (Section 2.3) (Adolphs, 2009; Bora et al., 2009; Brown et al., 2012; Brüne, 2005; Fitch et al., 2010; Frith and Frith, 2012; Kalkstein et al., 2010; Millan and Bales, 2013; Rushworth et al., 2013). By analogy to "neurocognitive impairment", deficits in social cognition are essentially refractory to existing antipsychotics yet, with the exception of some preliminary trials with oxytocin (Section 4.8), there have been comparatively *few* efforts to specifically redress the compromised social cognition of schizophrenia (Green et al., 2012; Meyer-Lindenberg et al., 2011; Millan et al., 2012). This is unfortunate since impaired social cognition has grave repercussions for functional outcome and may drive other symptoms, including NS (Section 2.2) (Brüne, 2005; Foussias et al., 2014; Green et al., 2008, 2012; Hoe et al., 2012; Millan et al., 2012).

The NS of schizophrenia, which encompass blunted affect, poverty of speech (alogia), amotivation, anticipatory anhedonia

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