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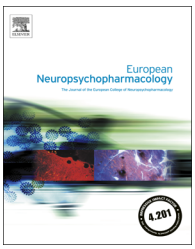

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Genetically modified mice related to schizophrenia and other psychoses: Seeking phenotypic insights into the pathobiology and treatment of negative symptoms

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Abstract
Modelling negative symptoms in any animal model, particularly in mice mutant for genes related to schizophrenia, is complicated by the absence of the following key elements that might assist in developing validation criteria: clinical clarity surrounding this symptom constellation; any clear association between negative symptoms and pathological signature(s) in the brain; and therapeutic strategies with material clinical efficacy against these symptoms. In this review, the application of mutant mouse models to the study of negative symptoms is subjected to critical evaluation, focussing on the following challenges: (a) conceptual issues relating to negative symptoms and their evaluation in mutant models; (b) measurement of negative symptoms in mice, in terms of social behaviour, motivational deficits/avolition and anhedonia; (c) studies in mutants with disruption of genes either regulating aspects of neurotransmission implicated in schizophrenia or associated with risk for psychotic illness; (d) the disaggregation of behavioural phenotypes into underlying pathobiological processes, as a key to the development of new therapeutic strategies for negative symptoms. Advances in genetic and molecular technologies are facilitating these processes, such that more accurate models of putative schizophrenia-linked genetic abnormalities are becoming feasible. This progress in terms of mimicking the genetic contribution to distinct domains of psychopathology associated with psychotic illness must be matched by advances in conceptual/clinical relevance and sensitivity/specificity of phenotypic assessments at the level of behaviour.

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1. Introduction

Patients with schizophrenia can exhibit persistent negative symptoms, which include decreased emotional expression, reduced goal-directed motivational behaviour, poverty of speech and social withdrawal (Stahl and Buckley, 2007; Tandon et al., 2009; Strauss et al., 2011). Though lacking the florid nature of positive psychotic symptoms, negative symptoms, together with cognitive dysfunction, are more pernicious in their impact and have been linked with impairment across numerous indices of functional status, including ratings of community functioning and performance-based measures of social skills (Patterson et al., 2001; Kurtz et al., 2005, 2013). Understanding of the pathobiology of negative symptoms, as well as the development of relevant preclinical models, has been hampered by continuing lack of clarity regarding the nosological status of primary, enduring negative symptoms and their relationship to a putative 'deficit syndrome' and to secondary, transient negative symptoms (O'Tuathaigh et al., 2010b; Keshavan et al., 2011).

Clinical research suggests that negative symptoms may not represent a unitary construct. Specifically, the factor structure of negative symptom scale items suggests two distinct factors, one factor reflecting *diminished expression* [comprising reduced affect and poverty of spontaneous speech], the other reflecting *volitional impairment* [including motivational deficits and social withdrawal] (Blanchard and Cohen, 2006; Kirkpatrick et al., 2011; Strauss et al., 2012, 2013). The former factor has been selectively associated with a number of clinical variables and functional deficits, including olfactory dysfunction (Malaspina and Coleman, 2003), longer duration of untreated psychosis (Malla et al., 2002) and reduced medication compliance (Tattan and Creed, 2001). It is unclear which symptom category is more strongly associated with worse premorbid function and functional outcome (Gur et al., 2007; Strauss et al., 2013). Improved investigation of pharmacotherapeutics strategies for addressing negative symptoms might accrue from selective targeting of each of these dimensions separately (Foussias and Remington, 2010).

Early conceptualisations of negative symptoms in schizophrenia included diminished hedonic function (for review, see Strauss and Gold, 2012). However, recent studies have demonstrated intact hedonic experience in schizophrenia and propose that an apparent reduction in capacity for pleasure may reflect disruption of reward computation and reward-seeking behaviour (Gard et al., 2007; Gold et al., 2008, 2013). Experimental studies have demonstrated deficits in reward-related learning, in addition to reduction in facilitation of behaviours oriented towards reward, in schizophrenia patients with negative symptoms (Gold et al., 2013). This distinction reflects the oft-cited dissociation between anticipatory motivation and hedonic reaction (i.e. 'wanting' vs. 'liking'). Deficits in reward-related processes in schizophrenia will reduce the propensity of a patient with schizophrenia to engage in goal-directed actions for rewards, regardless of whether the reward is enjoyed when obtained (Der-Avakian and Markou, 2012). A further challenge endures in that symptoms such as anhedonia are considered a 'core' clinical feature not only of schizophrenia but also of depression, with a pathobiology that may transcend these diagnostic categories (Treadway and Zald, 2011; Der-Avakian and Markou, 2012).

Deficits in social cognition, in particular emotion processing and *Theory of Mind* (the capacity to understand perspectives of others), have been documented in individuals across a number of measures (Bora et al., 2009; Kohler et al., 2010; Green and Horan, 2010; Green et al., 2012). Social cognition may represent a factor distinct and separable from negative symptoms (Mancuso et al., 2011), although this dissociation may not extend to all measures of social cognition (Kohler et al., 2010). Factor analysis has indicated that social cognition and neurocognition are better regarded as a single construct when predicting functional outcome mediated by clinical symptoms (Rabinowitz et al., 2012; Lin et al., 2013).

Existing antipsychotic medications are effective primarily in amelioration of positive and to some extent disorganisation symptom domains but exert little or no effect against both negative symptoms and cognitive impairment (Murphy et al., 2006; Tandon et al., 2009, 2010). Neither first- nor second-generation antipsychotic drugs, where therapeutic efficacy is primarily based on antagonism at the dopamine (DA) D2 receptor (Waddington et al., 2011), ameliorate negative symptoms in patients (Stahl and Buckley, 2007; Keefe et al., 2007; Swartz et al., 2007). The absence of appropriate pharmacotherapeutic strategies reflects the inadequacy of our knowledge of the pathophysiology of negative symptoms; improved understanding of the neurobiological bases of specific domains of psychopathology will both allow us to develop better preclinical models and increase the likelihood of developing treatments for treatment-resistant symptom dimensions (Keshavan et al., 2008; Tandon et al., 2010; Waddington et al., 2012).

When discussing how to establish the validity of any preclinical model of negative symptoms in schizophrenia, the scale of the undertaking soon becomes very clear (Lipska and Weinberger, 2000; Arguello and Gogos, 2006; Powell and Miyakawa, 2006; Low and Hardy, 2007; O'Tuathaigh et al., 2007a, 2010b). Establishing *face validity* [phenomenological similarity between behaviours modelled in the animal and the negative symptoms of schizophrenia] is hampered by uncertainty about whether some of the core features of the disorder are conserved across species (O'Tuathaigh et al., 2007a, 2010b; Jones et al., 2011). As indicated above, this issue is compounded by inadequate conceptualisation of what constitutes negative symptoms; additionally, this reflects clinical heterogeneity across patients with negative symptoms, as well as the acknowledged psychopathological overlap with symptoms observed in depression, Parkinson's disease, autism spectrum disorder (ASD) and other disorders. *Predictive validity* [the ability of a model to predict therapeutic efficacy of compounds used to treat symptoms in patients] is hampered by the absence of any compounds which have material clinical efficacy against negative symptoms. Establishing *construct validity* [whereby the features observed in an animal model share a neurobiological basis with symptoms in patients] is challenging, due to paucity of evidence concerning the underlying pathophysiology. Additionally, *aetiological validity* might be established by recreating mechanisms/processes in the animal which initiate the disease in humans (Nestler and Hyman, 2010). In the case of a less complex disorder, this might involve introducing