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Modelling the neuromotor abnormalities of psychotic illness: Putative mechanisms and systems dysfunction

John L. Waddington [a,b,*], Colm M. O'Tuathaigh [c]

[a] Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland
[b] Jiangsu Key Laboratory of Translational Research and Therapy for Neuro-Psychiatric-Diseases, Department of Pharmacology, College of Pharmaceutical Sciences, Soochow University, Suzhou, China
[c] School of Medicine, University College Cork, Cork, Ireland

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ABSTRACT

Limitations in access to antipsychotic-naïve patients and in the incisiveness of studies that can be conducted on them, together with the inevitability of subsequent antipsychotic treatment, indicate an enduring role for animal models that can inform on the pathobiology of neuromotor abnormalities in schizophrenia and related psychotic illness. This review focusses particularly on genetically modified mouse models that involve genes associated with risk for schizophrenia and with mechanisms implicated in the neuromotor abnormalities evident in psychotic patients, as well as developmental models that seek to mirror the trajectory, phenomenology and putative pathophysiology of psychotic illness. Such abnormalities are inconsistent and subtle in mice mutant for some schizophrenia risk genes but more evident for others. The phenotype of dopaminergic and glutamatergic mutants indicates the involvement of these mechanisms, informs on the roles of specific receptor subtypes, and implicates the interplay of cortical and subcortical processes. Developmental models suggest a criticality in the timing of early adversity for diversity in the relative emergence of psychological symptoms *vis-à-vis* neuromotor abnormalities in the overall psychosis phenotype. These findings elaborate current concepts of dysfunction in a neuronal network linking the cerebral cortex, basal ganglia, thalamus and cerebellum. Both findings in model systems and clinical evidence converge in indicating that any distinction between 'psychomotor' and 'neuromotor' abnormality is artificial and arbitrary due to a unitary origin in developmentally determined systems/network dysfunction that underlies the lifetime trajectory of psychotic illness.

1. Introduction

In *King Lear* (Shakespeare, 1605-6), Edmond states (Act V, scene 3) "Th' hast spoken right, 'tis true. The wheel is come full circle". The study of neuromotor abnormalities and associated pathology in schizophrenia echoes Edmond's insight into the circularity of how perceived wisdom can evolve. In the pre-neuroleptic era, abnormal motor phenomena were readily accepted as intrinsic to schizophrenia, both biologically and nosologically. In contrast, for long into the post-neuroleptic era, those same abnormal motor phenomena became equated primarily with adverse effects of essentially ubiquitous treatment with antipsychotic drugs, such that recourse to the perspective of the pre-neuroleptic era was deemed iconoclastic (see Waddington and Crow, 1988; Kendler, 2016; Berrios, this *Special Issue*). However, over subsequent years what was previously deemed iconoclastic has come 'full circle' in the renaissance of an important and now again mainstream aspect of the pathobiology of psychotic illness (see Whitty et al., 2009; Peralta and Cuesta, 2011; Hirjak et al., 2015; Walther, 2015) that is the topic of this *Special Issue*.

The diaspora of neuromotor abnormalities intrinsic to the disease process of schizophrenia has evolved from long-standing recognition in antipsychotic-naïve patients of *hypo*- and particularly *hyper*kinetic phenomena (for historical reviews, see Waddington and Crow, 1988; Berrios, this *Special Issue*; for systematic reviews and meta-analyses of contemporary studies, see Whitty et al., 2009; Pappa and Dazzan, 2009; Koning et al., 2010), through neurological 'hard' and particularly 'soft' signs (Whitty et al., 2009; Zhao et al., 2014), to motor deficits in children and adolescents before they evidence the diagnostic symptoms of psychotic illness (Dickson et al., 2012; Kindler et al., 2016; Burton et al., 2016) and which extend back to delayed attainment of developmental milestones in infancy (Filatova et al., 2017). Qualitative and newer quantitative techniques for clinic assessment of motor function, together with structural and functional neuroimaging, have been and continue to be of utility for investigating the pathobiology of such neuromotor abnormalities (Walther, 2015). However, limitations in access to antipsychotic-naïve patients and in the incisiveness of studies that can be conducted on them, together with (at least in most circumstances) the inevitability of subsequent antipsychotic treatment that obviates

* Corresponding author at: Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin 2, Ireland.
E-mail address: jwadding@rcsi.ie (J.L. Waddington).

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prospective/longitudinal studies, indicate an enduring role for animal models that can inform on these processes.

The now vast literature on animal models of schizophrenia at the level of behaviour (see Pletnikov and Waddington, 2016) focusses on 'psychomotor' phenomena [*i.e.* related to cognitive/motivational processes] rather than 'neuromotor' phenomena [*i.e.* involving more direct effects on primary neuronal processes]. Traditional models involve acute or chronic pharmacological treatment(s) in adolescent or young adult rodents, such as with the dopamine (DA) releasing agent amphetamine or the glutamate *N*-methyl-D-aspartate receptor (NMDA-R) antagonist phencyclidine. These compounds induce psychomotor effects related to psychosis, with neuromotor effects commonly held to reflect toxic doses. Attenuation of psychosis-related phenomena, including hyperactivity, by a second agent is held to indicate antipsychotic activity, with the induction of neuromotor effects by that second agent, when given alone, held to indicate liability for extrapyramidal side effects or toxic consequences. Thus, such models, when applied in this manner, have been of limited conceptual or practical utility in illuminating neuromotor phenomena intrinsic to the disease process of schizophrenia.

More contemporary models present different challenges. In genetically modified mouse models, neuromotor abnormalities in adolescent or young adult mutants may be interpreted as adverse phenotypic effects that can interfere with sometimes more subtle, psychosis-related phenotypes, including hyperactivity, and their pathophysiological characterisation. It has also been of concern that such neuromotor abnormalities may artefactually disrupt detection of amelioration of psychomotor phenotypes by putative therapeutic interventions. Where genetically modified mouse models manifest neuromotor abnormalities, they are typically eschewed *via* evaluations such as the Comprehensive Observational Assessment (COA; Irwin, 1968) and the SmithKline Beecham, Harwell, Imperial College, Royal London Hospital phenotype assessment (SHIRPA; Rogers et al., 1997), which focus on major health problems and/or severe sensory-motor defects, and assessment of motor coordination and balance on a rotating rod (rotarod; Buccafusco, 2009). Thus, genetically modified mouse lines having neuromotor phenotypes may be discontinued, rather than pursued to further illuminate neuromotor phenomena intrinsic to the disease process of schizophrenia.

Developmental models involve the administration to pregnant dams of substances that disrupt brain development in the fetus, such as methoxylazoxymethanol (MAM), which interferes directly with embryonic brain development (Dibble et al., 2016), or polyriboinosinic-polyribocytidilic acid (Poly I:C), which interferes indirectly with embryonic brain development *via* maternal immune activation (Meyer, 2014; Malkova et al., 2016). These treatments result in psychosis-related traits, including hyperactivity, in adolescent or young adult offspring that can be studied for pathophysiological mechanisms and/or sensitivity to therapeutic interventions. Such developmental models have not typically been investigated as thoroughly by COA- or SHIRPA-related protocols as have genetically modified mouse models, hence their capacity to illuminate neuromotor phenomena intrinsic to the disease process of schizophrenia is less clear, other than through the apparent absence of gross abnormalities.

The numerous dimensions of psychopathology in psychotic illness (van Os and Kapur, 2009) and of psychomotor behaviour in animal models that are held to relate to psychotic illness (*e.g.* prepulse inhibition, latent inhibition, social behaviour, cognition, operant responding; see Pletnikov and Waddington, 2016) are neither a focus of this *Special Issue* nor a topic of this review, subject to the exception of hyperactivity that may occupy the interface between psychomotor and neuromotor abnormality.

Given the paucity of studies that have utilised COA- and SHIRPA-related protocols or other specific approaches, which neuromotor behaviours in rodent models relate most closely to those evident in antipsychotic-naïve patients with psychotic illness and how might they be assessed? A recent study systematically evaluated 37 neuromotor abnormalities in 200 antipsychotic-naïve patients with schizophrenia spectrum disorders; on principle component analysis, the first three primary components resolved, in terms of % of variance in neuromotor abnormality explained, were *abnormal involuntary movements*, *hypokinesia* and *retarded catatonia* [marked underactivity, reported underactivity, negativism, poor/feeble compliance and mutism] (Peralta et al., 2010). Given that negativism, poor/feeble compliance and mutism are not readily accessible in animals, these findings indicate that (a) *abnormal involuntary movements* (dyskinesia) should be a primary focus for neuromotor abnormalities in rodent models and (b) 'activity' in rodents requires careful consideration in terms of the interface between *hypo*activity as an index of neuromotor abnormality and *hyper*activity as a putative index of positive, psychotic symptoms or neuromotor abnormality (van den Buuse, 2010; Rafter et al., 2016).

2. The enigma of *hyper*activity

When placed in a novel environment, most organisms, including humans and rodents, engage in spontaneous exploratory behaviour at a level higher than is evident in their usual, familiar environment. This *hyper*activity is commonly assessed in rodents *via* detection of breaks in photobeams directed across an open field with counting of those breaks over a fixed period of time or, less commonly, *via* ethologically-based techniques. Such behavioural *hyper*activity is held to reflect processes related to positive psychotic symptoms as: (a) spontaneous, exploratory *hyper*activity is mimicked by treatment of quiescent rodents with psychotomimetic agents such as amphetamine or phencyclidine; (b) both exploratory *hyper*activity and psychotomimetic-induced *hyper*activity are attenuated by pretreatment with D2 dopamine (DA) receptor antagonist antipsychotics; (c) direct stimulation of subcortical DAergic function induces *hyper*activity; (d) DAergic *hyper*function through subcortical D2 receptors has been identified as a pathophysiological substrate of positive psychotic symptoms; and (e) DAergic *hypo*function through cortical D1 receptors has been associated with negative symptoms and cognitive dysfunction (van den Buuse, 2010; Rafter et al., 2016; Howes et al., 2017; Weinstein et al., 2017).

However, quantification of photobeam breaks over a fixed, limited time-frame is a coarse index that obscures the ethological richness and psychological-neurological import of exploratory *hyper*activity. More extensive studies in mice have documented such *hyper*activity to consist of three factors: the amount of activity; the structure of that activity in terms of variability and predictability; and investigatory behaviour, which can be further decomposed into diversive *vs.* inspective exploration (Tanaka et al., 2012). Furthermore, exploratory *hyper*activity is not constant and changes qualitatively and quantitatively, typically diminishing in quantity over time in sometimes complex ways as the organism (animal or human) habituates to the novelty of the environment (Henry et al., 2010; Schomaker and Meeter, 2015).

These issues have been given clinical import by recent studies seeking to investigate exploratory activity in psychotic patients in a manner similar to that adopted in rodents. More specifically, Perry et al. (2009) have introduced a novel, human open field paradigm, namely the human Behavioural Pattern Monitor (hBPM). Patients and control subjects who participated in an experiment that involved wearing an ambulatory monitoring vest/accelerometer were asked to await the experimenter in the hBPM room; during this waiting period, they were assessed in terms of motor activity by accelerometer, changes in spatial location by video camera, and interactions with objects, drawers and window blinds. Relative to healthy volunteers, patients with schizophrenia and bipolar disorder each showed increased acceleration (bipolar > schizophrenia over the initial but not the late phase of assessment, indicating habituation in bipolar but not schizophrenia patients) and more variable/less ordered motor activity; schizophrenia patients increased their 2-dimensional (x, y) activity over assessment, while bipolar patients were initially more active but habituated more rapidly; both schizophrenia and bipolar patients moved in more direct, straight paths (bipolar > schizophrenia over the initial but not the late phase of

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