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

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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.

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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

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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

assessment, indicating more rapid habituation in bipolar than in schizophrenia patients); bipolar patients interacted with more objects in the hBPM than did schizophrenia patients or healthy volunteers. In overview, while both schizophrenia and bipolar patients showed diverse *hyper*activities, schizophrenia patients showed impaired habituation of their activities, while bipolar patients showed enhanced habituation of their activities with an increase in object interactions. That no evidence for *hypo*activity was found focusses interest on the disease process(es) of schizophrenia and bipolar disorder, rather than on antipsychotic and/or mood stabilising treatment (Perry et al., 2009, 2010). However, influence(s) therefrom cannot be excluded.

These findings emphasise the challenge of interpreting changes in 'activity' in the absence of antipsychotic treatment, whether *hyper-* or *hypo*activity, as psychomotor vs neuromotor processes on an either-or basis, or as an integrated, systems-based process related more fundamentally to the pathobiology of psychotic illness.

3. *Hyper*activity *vis-à-vis* dyskinesia

For the above reasons, this review focusses primarily on measures of *hyper*-/*hypo*activity *vis-à-vis* dyskinesia in animal models, supplemented by other neuromotor indices as may be available. The literature on dyskinesia both in humans and in rodents has long emphasised its prominent orofacial topography (Waddington, 1989, 1990). In rodents, while such studies focussed initially on models for antipsychotic drug-induced tardive dyskinesia (Ellison and See, 1989), it remained unappreciated that orofacial dyskinesia 'induced' by long-term antipsychotic drug administration in young adult rats is, in fact, the premature precipitation by antipsychotics of orofacial dyskinesia that occurs spontaneously as a consequence of maturation/ageing processes (Waddington, 1990). However, to evaluate such phenomena in antipsychotic-naïve mice was not possible using procedures available for studies in rats until our introduction of a technique that could resolve in mice four topographies of orofacial movement (vertical jaw movements, horizontal jaw movements, tongue protrusions, rapid movements of the incisors), together with movements of the head and vibrissae. This innovation allowed murine-based mutant techniques to be applied, in combination with other approaches, to study the complex neuronal circuitry involved in such dyskinesia (Tomiyama et al., 2001; Ikeda et al., 2015).

To maximise coherence, we focus here particularly on (a) genetically modified mouse models that involve (i) genes associated with risk for schizophrenia and (ii) mechanisms implicated in the neuromotor abnormalities evident in psychotic patients, and (b) developmental models that seek to mirror the phenomenology, trajectory and, to the extent known or surmised, the putative pathophysiology of psychotic illness; these are complemented by (c) other models that may inform on the principles and processes at issue.

4. Mutant mouse models: genes associated with risk for schizophrenia

4.1. DISC1

Since the original report linking the disrupted-in-schizophrenia 1 (DISC1) gene with psychosis and other serious mental illnesses, DISC1 has become perhaps the most intensively investigated individual gene in relation to schizophrenia. Although its precise role in schizophrenia has been subject to debate (Sullivan, 2013; Porteous et al., 2014), studies have identified DISC1 and its interactions with several proteins to play important roles in neurodevelopment and synaptic regulation (Porteous et al., 2014; Randall et al., 2014). Thus, several variant, including transgenic, modifications of DISC1 have been constructed in mice. These are associated with a variety of psychosis-related phenotypes, together with evidence for participation in gene-environment and gene-gene (epistatic) interactions, which include diverse effects on activity. In the minority of studies that also investigated neuromotor behaviour, primarily rotarod performance, this was unaltered (Lipina and Roder,

2014; Tomoda et al., 2016; see also O'Tuathaigh et al., 2017; Shevelkin et al., 2017); however, overexpression of the full-length human DISC1 transgene demonstrated increased activity with impaired rotarod performance (Trossbach et al., 2016). DISC1 and DISC1-interacting proteins are known to impact diversely on the regulation of DAergic function (Tomoda et al., 2016; Dahoun et al., 2017; O'Tuathaigh et al., 2017).

No DISC1 mutant line has yet to be evaluated for topographies of spontaneous orofacial dyskinesia or for influences on DAergic agonist-induced or antipsychotic-associated orofacial movements.

4.2. DTNBP1

Dystrobrevin-binding protein 1 (DTNBP1), more commonly known as dysbindin-1, regulates several aspects of early and late brain development and neuronal function, and variation in the DTNBP1 gene has been associated with risk for schizophrenia and, particularly, with cognitive dysfunction (Allen et al., 2008; Talbot et al., 2009; Petit et al., 2017). Mutant mice with disruption to dysbindin-1 present a complicated picture, with the bulk of studies deriving from a deletion that occurred spontaneously in a DBA/2J line, commonly known as Sandy (sdy) mice, in a region that resulted in loss of dysbindin-1; crossing this spontaneous mutation onto a preferred C57BL/6J background indicated a variety of psychosis-related phenotypes, including diverse effects on activity, with little evaluation of neuromotor function (Talbot, 2009; Petit et al., 2017). Dysbindin-1 is known to impact diversely on the regulation of DAergic function (Papaleo and Weinberger, 2011; Moran et al., 2014). Recently, we have shown that selective deletion of the dysbindin-1A isoform results in heightened initial exploratory activity with impairment in delay/interference-dependent working memory, in the absence of any neuromotor abnormality using COA/SHIRPA protocols (Petit et al., 2017).

No DTNBP1 mutant line has yet to be evaluated for topographies of spontaneous orofacial dyskinesia or for influences on DAergic agonist-induced or antipsychotic-associated orofacial movements.

4.3. Neuregulin-1

Neuregulin-1 (NRG1) is a broad family of epidermal growth factors that are associated with various neurodevelopmental and plasticity-related processes (Mei and Nave, 2014). The NRG1 gene has been associated replicably with risk for psychotic illness and with structural and functional neuroimaging abnormalities in psychosis (Allen et al., 2008; Mostaid et al., 2016, 2017). Thus, multiple variant, including transgenic, modifications of NRG1 have been constructed in mice. These are associated with a variety of psychosis-related phenotypes, together with evidence for gene-environment and gene-gene interactions, which include diverse effects on activity and variable effects on neuromotor behaviour, primarily using the rotarod (O'Tuathaigh and Waddington, 2015; O'Tuathaigh et al., 2017; Huang et al., 2015; Mostaid et al., 2016; Papaleo et al., 2016). NRG1 is known to impact diversely on the regulation of DAergic function (Moran et al., 2014; O'Tuathaigh et al., 2017). To illustrate these complexities, while mice with disruption of the immunoglobulin-like domain of NRG1 showed poorer performance in the rotarod task, mutation in the epidermal growth factor-like domain of NRG1 showed improved motor co-ordination in this task (Gerlai et al., 2000; Rimer et al., 2005). While one line of mice that over-expresses the NRG1 Type 1 isoform evidenced movement-related tremor and impaired performance on the rotarod (Deakin et al., 2009), two other such lines showed no abnormalities in posture, gait, motor coordination or tremor using a SHIRPA protocol (Kato et al., 2010) and intact performance on the rotarod (Yin et al., 2013).

On assessing four topographies of spontaneous orofacial dyskinesia, we have reported mutants with disruption of transmembrane-domain NRG1 to show an increase in movements of the incisors on comparison with wildtype controls (WT). Such movements, together with vertical jaw movements and tongue protrusions, were induced in WT by the D1-like agonist SKF 83959; this topography of SKF 83959-induced

orofacial movements in WT was transposed to one of increased horizontal jaw movements and decreased tongue protrusions in NRG1 mutants. These findings (Tomiyama et al., 2009) indicate that the schizophrenia risk gene NRG1 is involved in (a) the regulation not only of schizophrenia-related phenotypes but also in the emergence of orofacial movements, and (b) interactions with D1-like mechanisms in regulating the topography of orofacial dyskinesia.

In summary, there may be a modest relationship between NRG1 genotype and the emergence of neuromotor abnormality that is dependent on the nature, timing, expression pattern and magnitude of the NRG1 transgene; this may be particularly so for spontaneous orofacial dyskinesia.

4.4. Genome-wide association studies and copy number variants

The most extensive genome-wide association study (GWAS) to date has identified 108 loci to be associated with risk for schizophrenia, 83 of which had not been reported previously, with enrichment among genes expressed in brain, including DAergic and glutamatergic neurotransmission, and in immunity-related processes (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014); such SNP-based GWAS studies relate primarily to common genes of small effect. In contrast, the most extensive investigation of copy number variants (CNVs) to date has identified a global enrichment of CNV burden in schizophrenia, including genes associated with synaptic function and behavioural phenotypes in mice (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium; Psychosis Endophenotypes International Consortium, 2017); such CNV studies relate primarily to rare genes of large effect.

The majority of these genes have yet to be investigated in mutant mouse models that include assessment of neuromotor abnormalities. However, CNVs at 16p11.2 (duplication) and 22q11.2 (deletion or duplication) are associated with risk for psychosis (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium; Psychosis Endophenotypes International Consortium, 2017; Giaroli et al., 2014) as well as for autism spectrum disorder (ASD) and have been investigated in mutant mouse models that may illuminate new therapeutic approaches (Ellegood and Crawley, 2015; Blizinsky et al., 2016; Diamantopoulou et al., 2017). For example, general hyperactivity and increased frequency of motor stereotypies, phenotypes similar to those reported in mouse models of autism, have been documented in several lines with partial deletion of 16p11.2 (Portmann et al., 2014; Yang et al., 2015; Arbogast et al., 2016), while the opposite phenotype has been reported in mice carrying a 16p11.2 duplication (Arbogast et al., 2016). While neuromotor abnormalities other than ASD-related repetitive behaviour have not been a primary focus in these mutant mouse studies, further investigations on these and other psychosis-related CNV models may be informative.

5. Mutant mouse models: genes associated with neuromotor disorder

5.1. Dopaminergic mechanisms

Evidence continues to indicate DAergic *hyper*function through subcortical D2-like [D2, D3, D4] receptors as a pathophysiological substrate of positive psychotic symptoms and DAergic *hypo*function through cortical D1-like [D1, D5] receptors continues to be studied for putative associations with negative symptoms and cognitive dysfunction (Howes et al., 2017; Weinstein et al., 2017). As negative symptoms and cognitive dysfunction are domains of psychopathology that have been associated most reliably with neuromotor abnormalities in schizophrenia, particularly abnormal involuntary movements and Parkinsonian features (Waddington and Crow, 1988; Waddington, 1989; Peralta and Cuesta, 2011; Peralta et al., this Special Issue), model systems involving DA receptor subtype-mediated processes may be fruitful for understanding mechanisms of neuromotor dysfunction in schizophrenia (Waddington et al., 2005).

In relation to D1-like receptors, mutant mice with constitutive (developmental, whole brain) deletion of D1 receptors show habituation-dependent decreases in spontaneous horizontal jaw movements, tongue protrusions and incisor movements, with increased movements of the head and vibrissae, together with habituation-dependent hyperactivity. Deletion of D5 receptors results in an increase in vertical jaw movements, with decreases in horizontal jaw movements and movements of the vibrissae, together with subtle hypoactivity (Waddington et al., 2005, 2011).

In relation to D2-like receptors, deletion of D2 receptors results in an increase in vertical jaw movements, with decreases in tongue protrusions, incisor movements and head movements, together with hypoactivity; deletion of D3 receptors results in a habituation-dependent decrease in incisor movements, in the absence of effect on activity; deletion of D4 receptors is without effect on orofacial movements or activity. In summary, D1 receptors exert a fundamental role in promotion of spontaneous horizontal jaw movements and, to a lesser extent, of vertical jaw movements, tongue protrusions and incisor movements, in a manner that involves disruption to habituation processes, while D5 receptors play a lesser role in regulating these orofacial movements. In contrast, D2 receptors promote tongue protrusions, incisor movements and inhibit vertical jaw movements, while D3 receptors play a lesser role and D4 receptors a negligible role in regulating these orofacial movements. These findings (Waddington et al., 2011), in a designated test paradigm that excludes assessment of exploratory activity, are variably complemented by ethologically-based assessment of exploratory activity in an open field (Waddington et al., 2005).

While these constitutive mutant mouse models identify a particular role for D1 receptors and more subtle roles for other DA receptor subtypes in spontaneous orofacial movements, they involve deletion of these subtypes throughout the brain from conception. Yet greater information would be obtained from the use of conditional mutant mouse models that allow spatial and/or temporal control over the deletion. In mice with conditional, progressive loss of D1 receptors from the forebrain, including both cortical and subcortical regions, we found reductions in head and vibrissae movements (Tomiyama et al., 2011). In separate studies we have reported these mutants to show the additional neuromotor abnormality of disrupted gait (Kim et al., 2014). In mice with conditional, progressive loss of D1 receptors from their primary location on medium spiny neurons in the striatum, we found a marked reduction in horizontal jaw movements and reduction in tongue protrusions, which involve disruption to habituation processes, with increases in head and vibrissae movements (Tomiyama et al., 2011). Separately, we have reported these mutants to show the additional neuromotor abnormality of hindlimb dystonia (Gantois et al., 2007). In mice with conditional, progressive loss of D1 receptors from cortical pyramidal neurons, studies on orofacial movements are not yet available; however, we have reported these mutants to show the neuromotor abnormality of forelimb dystonia and impairment on the rotarod (Jiang et al., 2015).

Integrating all of the above findings reinforce a greater role for striatal D1 than for D2 receptors in the topographical regulation of orofacial movements. The co-occurrence of striatal D1-promoted facial (head and vibrissae) movements *and* striatal D1-inhibited oral (horizontal jaw and tongue) movements in mutant mice, together with other neuromotor abnormalities, may inform on the co-occurrence of Parkinsonian features *and* abnormal, involuntary movements in differing body regions (Peralta and Cuesta, 2011; Peralta et al., this Special Issue). Comparable studies on a conditional mutant line with upregulation of striatal D2 receptors (Simpson and Kellendonk, 2017) would be further informative on these issues.

5.2. Glutamatergic mechanisms

While long-standing and continually evolving insights into DAergic dysfunction in schizophrenia (typically hyperfunction through subcortical D2 receptors/hypofunction through cortical D1 receptors) occupies

'centre stage' in relation to pathobiology, a putative role for glutamatergic mechanisms (typically hypofunction through NMDA receptors) is no less prominent, whether as an alternative, complementary or interactive pathophysiological process (Poels et al., 2014; Howes et al., 2015). Therefore, model systems involving glutamate receptor subtype-mediated processes may also be fruitful for understanding mechanisms of neuromotor dysfunction in schizophrenia (Tomiyama et al., 2011).

Mutant mice with constitutive deletion of GluN2A receptors show a decrease in movements of the vibrissae, with disrupted habituation of head movements; deletion of GluN2B receptors results in increases in vertical and horizontal jaw movements and in incisor movements; deletion of GluN2D receptors results in increases in horizontal jaw movements, incisor movements and movements of the vibrissae, with a decrease in tongue protrusions, In summary, glutamate receptor subtypes exert fundamental but topographically distinct roles in regulating spontaneous vertical and horizontal jaw movements, incisor movements and tongue protrusions (Tomiyama et al., 2013). In contrast to findings following deletion of DA receptor subtypes, deletion of glutamate receptor subtypes was less likely to result in concurrent, differential effects on facial vs oral movements. Rather, GluN2A receptors primarily promoted facial movements, while GluN2B and GluN2D receptors primarily inhibited jaw and incisor movements. There are numerous additional glutamate receptor subtypes (Traynelis et al., 2010) that may repay similar studies.

5.3. GABAergic mechanisms

These putative DAergic and glutamatergic aspects of the pathobiology of schizophrenia are themselves complemented by long-standing interest in possible GABAergic dysfunction, whether as an alternative, complementary or interactive pathophysiological process (Cohen et al., 2015; Glausier and Lewis, 2017). Therefore, model systems involving GABA-mediated processes may also be fruitful for understanding mechanisms of neuromotor dysfunction in schizophrenia (Tomiyama et al., 2011).

Mutant mice with constitutive co-deletion of the proteins PRIP-1 and PRIP2, which regulate the assembly and trafficking of $GABA_A$ receptors, show a decrease in tongue protrusions, with disrupted habituation of vertical jaw, head and vibrissae movements (Tomiyama et al., 2010). In mice with constitutive deletion of the GABA synthesising enzyme GAD65, vertical jaw movements are reduced (Tomiyama et al., 2013). In summary, in contrast to DAergic and glutamatergic processes, $GABA_A$ receptor-mediated processes exert an important but more topographically restricted role by regulating spontaneous tongue protrusions and vertical jaw movements. $GABA_B$ receptor-mediated processes remain essentially unexplored in this context and may repay similar studies.

6. Developmental models

Given the weight of epidemiological and biological evidence that schizophrenia is a neurodevelopmental disorder associated with early developmental impairment but delayed emergence of psychotic symptoms (Waddington et al., 2012), alternative models focus on the effects of pre- or peri-natal insult on the development of a phenotype that mimics features associated with the trajectory of psychotic illness in humans.

6.1. MAM

Administration of the antimitotic compound methylazoxymethanol acetate (MAM) to a pregnant rat or mouse selectively impairs embryonic brain development (Moore et al., 2006; Dibble et al., 2016). Specifically, while very early exposure to MAM leads to marked microcephaly and gross neuromotor abnormalities, administration of MAM on gestational day (GD) 17 is associated with the emergence in young adulthood of schizophrenia-related structural, neurochemical and behavioural

effects; while exposure to MAM on GD17 did not alter spontaneous activity, it resulted in dysregulation of striatal and cortical DAergic and glutamatergic neurotransmission, with enhanced amphetamine-induced increase in locomotor activity and efflux of DA in the nucleus accumbens (Flagstad et al., 2004; Moore et al., 2006; Dibble et al., 2016). MAM exposure at GD15, but not GD17, was associated with increased levels of ataxia; however, MAM exposure at GD17 was associated with impaired performance on the rotarod and with spontaneous orofacial dyskinesia (Balduini et al., 1991; Moore et al., 2006).

6.2. PolyI:C

Early maternal exposure to the immune-stimulating agent polyinosinic:polycytidylic acid (PolyI:C) is associated with the emergence in offspring during young adulthood of schizophrenia-related structural, neurochemical and behavioural effects, with the phenotype depending on the timing of exposure (Meyer, 2014; Malkova et al., 2016): when administered on GD9, pups show reduced exploratory activity and heightened DAergic function in mesocorticolimbic regions; when administered on GD13–15, pups show impaired performance on the rotarod and ladder-rung test in adolescence that was less evident in adulthood (Aavani et al., 2015). Other studies have also demonstrated, in addition to psychosis- and autism-related behaviours, long-term effects of prenatal PolyI:C exposure on motor coordination in the rotarod, accompanied by age-dependent, postnatal loss of cerebellar Purkinje cells (Shi et al., 2009; Naviaux et al., 2013, 2014). A relationship between immune system dysregulation and psychosis extends to autoimmune processes, including anti-NMDA receptor autoantibodies, and such 'autoimmune psychosis' can present with various neuromotor abnormalities (Ellul et al., 2017). Thus, further investigations on putative mouse models (Kowal and Diamond, 2012; Kannan et al., 2016) may be informative.

7. Synthesis: modelling neuromotor abnormality that is integral to a disease process of cortical-subcortical network dysfunction

It has been argued from a clinical perspective (Whitty et al., 2009; Peralta et al., 2010; Waddington et al., 2012) that neuromotor abnormality, among which *hypo-* and *hyper*kinetic features, particularly abnormal, involuntary movements, constitute the most extensively investigated phenomena, appears integral to the disease process of schizophrenia and is evident even before the emergence of diagnostic psychotic symptoms in young adulthood and resultant treatment with antipsychotic drugs. The modelling studies reviewed here should be interpreted in this context and should also reflect increasing recognition of psychotic illness as disrespectful to our current nosology in terms of the complexity and continuous, dimensional nature of developmentally determined psychiatric traits, including psychosis (Owen, 2014; O'Tuathaigh and Waddington, 2015; Pletnikov and Waddington, 2016). By way of example, the gene Sema6A co-ordinates axon guidance, laminar connectivity, neuronal migration and dendrite development, with mutation of Sema6A resulting in subtle derangement of neuronal cytoarchitecture and connectivity between cortical and subcortical structures; we have reported such mutant mice to show not only hyperactivity with disruption of habituation, together with impairments in social dominance-related behaviour and working memory, but also subtle neuromotor abnormalities of impairment in gait and performance on the rotarod (Rünker et al., 2011; Håkansson et al., 2017).

On this background of Sema6A mutants as an exemplar, the challenge is to distil the model profiles considered here to identify, beyond their defining and overlapping psychosis-related phenotypes, putative mechanisms of neuromotor abnormalities. While such abnormalities are inconsistent and subtle in diverse DISC1 and DTNBP1 mutant lines, they are more evident in NRG1 mutants; this may reflect the greater range of phenotypic assessments applied and/or that individual risk genes do not confer comparable risk for all aspects of the psychosis

phenotype. The phenotype of DAergic, glutamatergic and GABAergic mutants directly indicates the involvement of these mechanisms, resolves the roles of specific DA and glutamate receptor subtypes, and implicates the interplay of cortical and subcortical processes in their manifestation. Findings from the MAM and PolyI:C models suggest *inter alia* 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 clinical phenotype for a given patient with psychotic illness.

Current concepts elaborate schizophrenia as a disorder of developmentally determined disconnectivity in cortical-basal ganglia-thalamo-cortical/cerebellar systems (Waddington et al., 2012; Friston et al., 2016), in a manner that includes dysfunction in DAergic (Dandash et al., 2017) and/or glutamatergic (Pratt et al., 2017) processes. Furthermore, studies (Perry et al., 2009, 2010) now indicate a 'grey' zone between psychomotor and neuromotor abnormalities in patients that interfaces 'activity' and its subsequent habituation with spontaneous *hypo-* and *hyper*kinetic motor phenomena. These concepts are consistent with the known pathobiology and clinical correlates of such neuromotor abnormalities, which continue to implicate a neuronal network linking the cerebral cortex, basal ganglia, thalamus and cerebellum, and of involuntary movements, which implicate dysfunction in a cortical-basal ganglia-thalamo-cortical network (Whitty et al., 2009; Zhao et al., 2014; Friston et al., 2016). For example, orofacial dyskinesia appears to involve the interplay of pattern generators for down-stream patterns of motor sequences with up-stream basal ganglia and thalamo-cortical regulatory mechanisms, under the influence of DAergic, glutamatergic and GABAergic mechanisms (Tomiyama et al., 2011; Waddington et al., 2011; Ikeda et al., 2015). Thus, both clinical evidence and findings in model systems converge in indicating that any distinction between 'psychomotor' and 'neuromotor' abnormality is artificial and indeed arbitrary due to a unitary origin in developmentally determined systems/network dysfunction that underlies the lifetime trajectory of psychotic illness.

Conflict of interest

Contributions

John Waddington and Colm O'Tuathaigh contributed to the conception and writing of this review, revising the manuscript and giving final approval of the version to be published.

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