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Review

Sensitive and critical periods during neurotypical and aberrant neurodevelopment: A framework for neurodevelopmental disorders

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ABSTRACT

During sensitive and critical periods, the brain undergoes significant plasticity from the level of individual synapses and neuronal networks up to the level of behaviour. Both sensitive and critical periods during neurotypical development of the young animal provide a framework to the early temporally-regulated modifications that occur in the nervous system.

In neurodevelopmental disorders (NDD), notably autistic syndromes and intellectual disability, children exhibit developmental delays in motor, social and sensory processes and often miss key developmental milestones. In corresponding genetic NDD mouse models, recent data reveal temporally-regulated and in some cases, transient impairments in many neuronal and behavioural phenotypes during development. However, the mechanisms underlying these impairments in NDDs and their potential links with neurobiological mechanisms governing neurotypical development are not fully investigated. This article highlights the potential for the use of known critical and sensitive periods during vertebrate development to investigate and advance our understanding of the neural bases underlying impairments in these developmental disorders of the nervous system.

Contents

1. Introduction

Building a brain, a complex neuronal computer with a repertoire of behaviours and the potential to learn, requires a carefully choreographed sequence of steps. The process of brain development is determined by distinct developmental stages of gene expression, intrinsic neuronal activity and molecular guidance cues (Chilton, 2006; Marin et al., 2010), combined with the influence of external factors including resources from the mother during embryonic stages (Zimmerman and Connors, 2010). Time-limited developmental stages in neuronal migration, circuit formation and synaptic refinement are key to form the adult brain. Using the

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rodent brain as a model system, much is known about the neural basis of these distinct developmental stages, known as critical or sensitive periods. To-date, research has largely focused on elucidating the neural mechanisms underlying critical and sensitive periods of normal or neurotypical brain development and behaviour (Hensch, 2004; Knudsen, 2004). Clear evidence is shown for the existence of critical and sensitive periods across many vertebrate species, including pre- and postnatal stages in the primate brain comparable to those observed in the rodent (Workman et al., 2013).

More recently, animal models for monogenic neurodevelopmental disorders have shown specific impairments during well-established critical periods. These data have led to the notion that impairments underlying neurodevelopmental brain disorders have their onset during restricted critical or sensitive periods (Kroon et al., 2013; LeBlanc and Fagiolini, 2011; Martin and Huntsman, 2012; Meredith et al., 2012; Wang et al., 2014). This mini-review will outline the idea that our existing knowledge of sensitive and critical periods can be used as a framework to investigate potential mechanisms underlying NDDs and as a guide for elucidating the developmental time periods during which misregulation may first occur.

1.1. Critical and sensitive periods for brain development

During the development of an organism, critical and sensitive periods are time windows during which the system is most subject to change (Hensch, 2004, 2005; Johnson, 2005; Michel and Tyler, 2005). During these time windows, plasticity of specific physiological or behavioural phenotypes are heightened relative to other developmental stages. A critical period is a restricted time window during which the system is most responsive for an essential developmental change to occur, its absence causing a permanent modification in brain and behaviour. Critical periods are limited during a specific time window and after their closure, the phenotype is classically thought not to be malleable – but see, e.g. (Oberlaender et al., 2012; Pizzorusso et al., 2002) for somatosensory and visual manipulations in adulthood. The distinction between critical and sensitive periods can be subtle: Historically, critical periods have been used to describe brain circuit-based phenotypes including ocular dominance in the visual system or synaptic plasticity in the developing somatosensory cortex (Fox et al., 2000; Hensch, 2004). Sensitive periods, on the other hand, are often referred to as time windows during which exposure of the organism to external factors or experience modulates the emergence of specific behaviours. Classic examples include filial imprinting in young birds whereby they form a social attachment to their mother or equivalent during the first few days post-hatching (Horn, 2004; Lorenz, 1935).

These restricted time periods occur along different temporal trajectories from filial imprinting within the first few days of life in the precocial chick, to visual development in humans, where poor vision in the condition amblyopia can be corrected over a period of months and even years but only during childhood. Critical and sensitive periods provide a framework to map out time windows for great change and plasticity of the brain as it grows normally. However, many now believe that these periods also represent points of particular vulnerability in the developing brain. A small change in gene expression, external growth factor or altered neuronal activity pattern in the nervous system due to intrinsic or extrinsic sources can have a major influence upon the developmental trajectory of the organism, and can potentially lead to specific neurodevelopmental impairments.

1.2. Developmental aspects of NDDs

Neurodevelopmental disorders (NDDs) are caused by impairments during growth of the nervous system that cause or lead to dysfunction at neuronal and sensory or behavioural levels (Goldstein and Reynolds, 1999). NDD impairments usually manifest at birth or during infancy and can affect multiple functions including cognitive processing, language, emotion and motor control (Zoghbi and Bear, 2012). Many syndromes are classified as NDDs; for the purposes of this article, focus will be limited to intellectual disability (ID) and autism spectrum disorders (ASD). However, the hypotheses discussed may well apply to other disorders with clearly dysregulated developmental profiles. For ID and ASDs, the onset and progression of the disorder can be striking: parents and clinicians report a series of missed developmental milestones during the first few years of life including speech impairments, motor delays and irregular social interactions for some children (Geschwind and Levitt, 2007; Kau et al., 2000). For example, hypotonia and early onset delays in motor skills are characteristic for many monogenic NDDs including Angelman and Fragile X syndromes (Clayton-Smith and Laan, 2003; Kau et al., 2000; Williams et al., 2006). Furthermore, deficits in speech development and difficulties with social communication & interaction are common to both Angelman and Fragile X syndromes, either characterised as core symptoms or as part of an associated ASD (Amiet et al., 2008; Gillberg and Billstedt, 2000). Even if transient in nature, the effects of these developmental delays may also extend beyond the initial appearance to cause later disruptions. This concept, known as 'sleeper effects' can be seen in the visual system where early transient impairments in vision caused by cataracts disrupt the normal patterned activity necessary for aspects of visual perception later on in adulthood (Maurer et al., 2007).

It is not just syndromic NDDs with a monogenic cause that show clear developmental onset and progression: other nonsyndromic NDDs or those induced by environmental insults delineate similar dependence upon brain developmental stages. For example, significantly higher than normal incidences of spina bifida and ASD diagnosis occur in children whose mothers took the anti-epileptic drug valproic acid (VPA) during pregnancy (Christensen et al., 2013). Specifically, incidence of malformations in foetal valproate syndrome is highest if exposure occurs during the first trimester (Lindhout and Omtzigt, 1992). These effects are verified in a rodent model of VPA exposure where injection of VPA into the mother at embryonic day (E)12.5 causes an increased incidence of neural tube closure difficulties in the offspring and later emergence of autistic phenotypes in the form of stereotypy and hyperactivity (Dawson et al., 2006; Schneider and Przewlocki, 2005).

Regardless of the underlying genetic or environmental cause for an NDD, the early developmental onset and delays in progression are common across syndromic and nonsyndromic conditions. By focusing on the developmental misregulation during specific critical periods, this article proposes that the known neural mechanisms regulating these critical periods may guide investigation into the neural changes that may underlie the misregulated phenotypes in NDDs.

1.3. Synaptic basis of NDDs

Many NDDs are heterogeneous disorders, with heritable but also multiple de novo mutations involved in ID and ASD (Neale et al., 2012; O'Roak et al., 2012; Sanders et al., 2012). Of those genes known from monogenic syndromes and those from large genome-wide-association-studies for ASD, a significantly high proportion of candidate targets are located at the pre- or postsynaptic compartments or are known to directly regulate synaptic functions in neurons (Kang et al., 2011; Ruano et al., 2010; van Bokhoven, 2011; Voineagu et al., 2011). These observations have led to the term 'synaptopathies' to describe the multitude of conditions, including ID and ASD, that directly affect synaptic processing and plasticity (Brose et al., 2010). At the anatomical level, these synaptic effects

in NDDs can be clearly observed in post-mortem tissue as dysmorphology of dendritic spines, an abundance of immature filopodia and changes in protrusion density (Kaufmann and Moser, 2000; Purpura, 1974). Furthermore, where animal models exist for monogenic syndromes, these spine and filopodia dysmorphologies can be confirmed across different brain regions and in both young and old brains (Portera-Cailliau, 2012; Ramakers, 2002). A well-studied example of an NDD that resembles these phenotypes is the mouse model for Fragile X syndrome. Fragile X syndrome is an X-linked disorder causing impaired cognitive processing with partial comorbidity for ASD in around one third of people with the syndrome (Bagni et al., 2012). The Fmr1 gene on the X chromosome is preceded by an expanded CGG trinucleotide repeat sequence in Fragile X syndrome, leading to hypermethylation of the gene and downregulation or no production of Fragile X mental retardation protein (FMRP) (Bagni and Greenough, 2005). FMRP has many known functions, predominantly as an mRNA binding protein and regulator of synaptic protein synthesis (Bear et al., 2004). Fmr1 triplet nucleotide repeats are conserved across many vertebrate species (Eichler et al., 1995) and an Fmr1-knockout mouse model for the syndrome was made two decades ago (Bakker et al., 1994). Aberrant spine morphology and/or density is observed in both human post-mortem tissue and brain samples from the Fmr1-KO mouse, with typical increased occurrence of immature spine and filopodia and in some brain regions, an increased density of synaptic protrusions (Portera-Cailliau, 2012). FMRP binds to over 800 different mRNA targets in the adult brain, (Darnell et al., 2011) and alters expression of many synaptic proteins (Adusei et al., 2010; Klemmer et al., 2011). Furthermore, at the synapse, many synaptic function and plasticity properties are affected (Meredith and Mansvelder, 2010; Pfeiffer and Huber, 2009). FMRP targets distinct mRNA sequences throughout the nervous system and these targets can be grouped on the basis of physiological functions, such as GTPase regulatory activity, or on subcellular and synaptic location (Ascano et al., 2012; Darnell et al., 2011). Thus, NDDs are often but not exclusively grouped as synaptopathic disorders, dysregulating synapse structure and function in the brain.

1.4. Utilisation of critical periods for investigating mechanisms underlying NDDs

This article proposes an interaction between critical periods and NDDs: namely, the temporal onset and symptom progression for a disorder may be caused by misregulation of critical periods for synaptic brain circuitry that subsequently alter or severely disrupt sensitive periods for behaviour. At the synaptic level, abnormalities in postsynaptic spines and filopodia occur across many different brain regions in both human post-mortem brain samples and in genetic mouse models for corresponding syndromes. Embryonic and early postnatal spine dysmorphology in these disorders supports the hypothesis that abnormal patterns of synaptic maturation and distribution are not necessarily a *consequence* of impaired cognitive and sensory processing. Rather, they indicate a *causal* stage in the development of the disorder whereby presymptomatic aberrations occur in mechanisms regulating synaptic circuitry, before significant cognitive and behavioural dysfunction.

Critical period dysregulation may therefore pinpoint the key developmental stages at which synaptic circuits in the brain are affected in NDDs and which potential underlying synaptic mechanisms are impaired. Should these delayed critical periods occur within prenatal periods of development, it would imply dysregulation of brain circuits at much earlier stages than are currently known for NDDs. Further, by showing early dysregulation of subcortical circuits in the brain, it may challenge the definition of a 'presymptomatic' stage for specific syndromes if changes in foetal or neonatal brain circuits are observed. For human NDD syndromes, the finding of early critical period dysregulation in an equivalent rodent model may guide investigation towards prenatal time periods of brain formation that are not currently studied in the clinic. However, to enable translational studies to humans from rodents models, valid data are needed to compare similar critical period stages from one species to another. Brain development and maturation comparisons between species is based upon a number of indicators including overall brain growth, timing of neuro- and gliogenesis, neuronal migration biomarkers and synapse formation (Romijn et al., 1991; Semple et al., 2013; Workman et al., 2013). By combining these factors, estimations of comparative neurodevelopmental stages can be made across mammalian species (Clancy et al., 2007, www.translatingtime.net). For example, neurogenesis in rodent brain from E18 to E21 is proposed to compare with human foetal neurogenesis stages from week 8/9 to week 15/16 (Bayer et al., 1993). However, there are far fewer data comparing defined critical periods documented in rodent species to their human equivalent stages. Furthermore, just as critical periods in rodent development occur in a sequential or differential temporal pattern across the brain, so do 'markers' such as neurogenesis differ slightly in their timing from brain region-to-region, making precise regional comparisons between brains of differing species challenging. Notwithstanding the challenges of making these cross-species comparisons, the implications of such measurements at early developmental stages in NDD rodent models would be significant for in utero and neonatal screening and raise possibilities for the timing of therapeutic interventions in the future.

2. Evidence for misregulated critical periods and developmental time windows in animal models for NDDs

From many different mouse models for a variety of NDDs, consistent spine dysmorphologies or alterations in the pattern of synaptic protrusions are reported (Galvez and Greenough, 2005; Maynard and Stein, 2012; Meikle et al., 2007; Powell et al., 2012; Ramakers, 2002; Sato and Stryker, 2010; Yashiro et al., 2009). Most dysmorphologies are reported during adulthood at behaviourally-relevant stages or around 2–3 postnatal weeks old when the cortex and hippocampus undergo periods of heightened synapse remodelling during circuit formation (Portera-Cailliau, 2012). However, there are increasing data showing developmentally-regulated synaptic phenotypes across multiple ages in mouse models for NDDs and in certain cases, the existence of transient phenotypes that may be comparable to changes during known critical periods.

Prominent examples of such phenotypes can be found in the somatosensory system of the monogenic Fmr1-KO mouse model for the intellectual disability disorder, Fragile X syndrome. During normal or 'neurotypical' development of sensory systems in the vertebrate brain, spatiotemporal regulated patterns of synaptic connectivity and synapse plasticity exist. From developmental stages beginning in utero, brainstem axonal pathways make connections to thalamic nuclei, thalamic projections grow into the cortex and finally corticocortical circuits are established (Feldmeyer et al., 2013; Fox, 2002). These regulated developmental periods occur in a wave-like, sequential fashion from region to region and across interregional layers. For example, in the rodent somatosensory system, thalamocortical excitatory projections to layer 4 cortical neurons are able to undergo synaptic plasticity during a restricted period from postnatal days 3 to 7 (Crair and Malenka, 1995). Layer 4 neurons begin to make functional synaptic connections with pyramidal neurons in layers 2 and 3 from postnatal day 5 onwards and are highly plastic during the second and third postnatal weeks, coincident with the peak period for cortical synapse formation and refinement (Bender et al., 2003; Maravall et al., 2004; Mierau et al., 2004). In the Fmr1-KO mouse, time-restricted alterations are observed in the thalamocortical pathway: increased

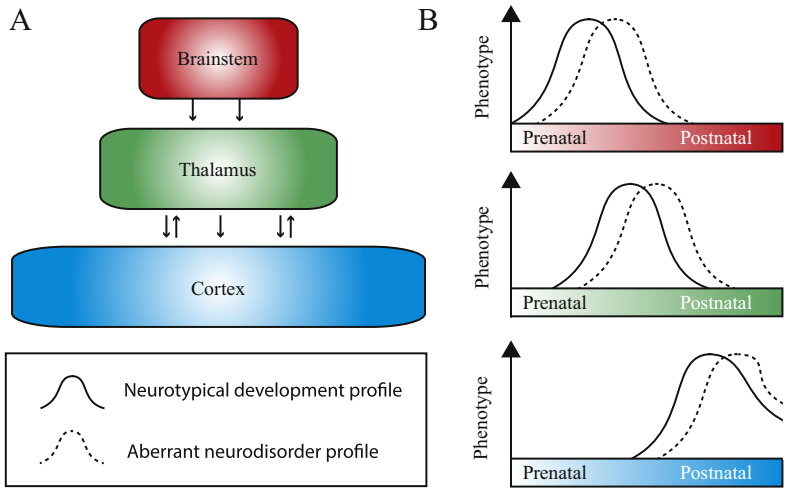

Fig. 1. Sequential disruption of critical periods across the brain in neurodevelopmental disorders. (A) Each region (brainstem, thalamus, cortex) forms functional monosynaptic projections to the next 'higher' brain region. (B) For each brain region, the neurotypical developmental profile of a specific phenotype is illustrated. This occurs with a restricted 'critical period' of time. Phenotype can refer to a variety of changes, from the level of expression of a particular gene, to a synaptic response or property or to a behavioural phenotype. For the same phenotype, the neurotypical profile occurs slightly later in each region from brainstem to cortex, following an established developmental sequence. For NDDs, the aberrant neurodisorder profile illustrates a potential developmental delay in the phenotype for each region that normalises shortly after the close of the critical period. Thus, the aberrant phenotype for each region during each critical period is transient.

NMDA:AMPA ratios and altered synaptic plasticity of layer 4 neurons occur during the first but not by the end of the second postnatal week of development (Harlow et al., 2010). In addition to excitation, maturation of local GABAergic inhibition on layer 4 neurons is also delayed at the end of the normal critical period of P10 (Daw et al., 2007) but then normalises to WT levels by P15 (He et al., 2014). By the second postnatal week, following closure of the normal critical period for the thalamocortical pathway, Fmr1-KO mice exhibit impairments in the layer 4 projections to layer 2/3 pyramidal neurons. Here, decreased synaptic connectivity and diffuse branching of axons occurs transiently, only to be normalised by the third postnatal week of development (Bureau et al., 2008). During the second postnatal week, Fmr1-KO mice display additional cortical impairments with a delay in the maturity of synaptic protrusions from transient filopodia to more mature longer-lasting spines (Cruz-Martin et al., 2010). However, by one month of age, both immature spine morphologies in the somatosensory cortex and dynamic spine turnover are normalised (Cruz-Martin et al., 2010; Nimchinsky et al., 2001). Thus, there are transient and developmentally-delayed phenotypes in the somatosensory cortex of Fmr1-KO mice during known critical periods for specific synaptic circuits. These delayed or transient phenotypes are by no means restricted to this one brain region but are present in other cortical and hippocampal regions for the Fragile X model (see (Meredith et al., 2012) for summary), in the amygdala (Vislay et al., 2013) and in the Drosophila model of Fragile X syndrome (Gatto and Broadie, 2009). Of note, misregulations of critical periods are observed in other NDD models (see summary in (LeBlanc and Fagiolini, 2011)) with even the opposing phenotype of precocial synapse maturation during a known thalamocortical period observed in the Syngap1 gene mutant mouse (Clement et al., 2013).

There is a scarcity of data reporting longitudinal studies into adulthood in the Fmr1-KO or other NDD mouse models. However, two overlapping studies of spine morphology in layer 5 pyramidal neurons in the somatosensory cortex of the Fmr1-KO mouse reveal that the immature spine phenotype observed at the first and second postnatal weeks but normalised by one month of age, does reappear after two months of age (Galvez and Greenough, 2005; Nimchinsky et al., 2001). Intriguingly, the reappearance of an immature phenotype in the adult reflects findings in the DSCAM mouse model for Down syndrome (Maynard and Stein, 2012), hinting that there may be many more transient and developmentally-regulated phenotypes to discover in other mouse models for NDDs.

2.1. Multiple or sequential disruption of critical periods

Based on evidence from the Fmr1-KO mouse and other examples in NDD models, current findings point towards a sequential disruption of critical periods across thalamic and cortical regions that could potentially be extended to subcortical brainstem circuits (Fig. 1). During normal development, each of the three regions (brainstem, thalamus, cortex, Fig. 1A) are directly connected via monosynaptic projections that mature in synaptic function and exhibit synaptic plasticity during specific periods from pre- to postnatal timepoints in the rodent brain. Specific phenotypes, for example, expression of a receptor subunit or other intracellular signalling molecule, spine morphology or synaptic plasticity occur within a critical period of development for each region normally (solid lines, Fig. 1B). In an NDD model, these phenotypes are dysregulated in a time-specific and spatially-restricted pattern relative to the normal critical period for that brain region (dotted lines, Fig. 1B). For each region, a sequence of developmental delays could progress across the brain as the critical periods open and close during maturation. To investigate the possibility for consequential developmental delays in brain maturation arising from earlier misregulation of a critical period, there are increasingly more tools available to test this proposal in rodent models. Critical periods may be manipulated by application of subunit-specific receptor ligands that can cross the placenta from mother to pups or be given directly to pups during postnatal periods. Time-dependent pharmacological blockade of a subtype of glutamatergic receptors restricted to either a prenatal period or the first postnatal week of rodent brain development has been demonstrated as a model for schizophrenia, whereby this intervention disrupts NMDA receptor function and leads to misregulation of fast-spiking interneuron abundance and function later in life (Abekawa et al., 2007; Jones et al., 2014). However, the pharmacological intervention is not restricted to a particular brain region but dependent upon target receptor expression patterns. A more localised approach is the combination of brain region- and promoter-specific Cre mouse lines with conditional KO mouse lines for NDDs. Use of a KO mouse model for the Syngap1 gene, a commonly mutated neuron-specific gene in sporadic

cases of ID, crossed with the Emx1-ires-Cre driver line that targets glutamatergic neurons (and glia) in the forebrain demonstrated that brain region-specific disruption of Syngap1 in excitatory neurons only was sufficient to induce similar behavioural changes and a reduced seizure threshold as observed in young adult conventional Syngap1 mutant mice (Ozkan et al., 2014). These behavioural phenotypes correlated with increased excitatory synaptic function in adult prefrontal cortex pyramidal neurons. Hyperexcitability was only induced by Syngap1 disruption during early development but not adulthood – a developmentally-dependent disruption reflecting that observed in the hippocampus if Syngap1 was haploinsufficient during the critical period of the first two postnatal weeks (Clement et al., 2012). In the coming years, adaptation of a relatively novel pharmacogenetic approach of 'Designer Receptors Exclusively Activated by Designer Drugs' (DREADDs, (Lee et al., 2014)) could also enable targeted and transient manipulations prior to, during or following closure of critical periods in many monogenic NDD models.

Currently, very little is known regarding subcortical brain circuitry in NDDs. Given the subcortical expression of many genes for monogenic NDDs from prenatal developmental periods onwards (Kang et al., 2011; Kroon et al., 2013, Allen Institute for Brain Science, www.developingmouse.brain-map.org), it is plausible that misregulation of these genes can cause subcortical phenotypes during the earliest stages of development in specific syndromes. Application of the hypothesis for dysregulated critical periods in brainstem regions (Fig. 1) could guide investigation within subcortical circuits during specific time-windows of pre- and postnatal development for such phenotypes in mouse NDD models. Indeed, in the MECP2 KO mouse model for Rett syndrome, changes in GABAergic inhibitory transmission and a reduction of GABA-A receptor subunits are already reported in ventrolateral brainstem within the first postnatal week (Medrihan et al., 2008). More recently, a transient embryonic delay in the multipolar-to-bipolar transition of neurons in developing cerebral cortex is reported in the Fmr1-KO mouse model (LaFata et al., 2014). Thus, there are likely to be other embryonic or early postnatal phenotypes in NDD mouse models that are, as yet, undiscovered.

2.2. Linking spatial and temporal aspects of gene expression to critical period disruption

What could explain the underlying misregulation or appearance of impairments in NDDs during known critical periods? And are there common synaptic mechanisms that are affected by NDDs that underlie critical periods during normal development? For many synaptic phenotypes, some of the underlying cellular and molecular mechanisms determining the onset, maintenance or closure of a phenotype during normal development are known. For example, onset and closure of the critical period for ocular dominance in the rodent visual cortex can be altered by changing GABAergic inhibition: onset of plasticity can be delayed by deletion of the GABAergic synthase, GAD65 (Hensch et al., 1998), or can be brought forward by introduction of benzodiazepines just after eye-opening (Fagiolini and Hensch, 2000). An imbalance between inhibitory and excitatory signalling in the brain is proposed to underlie many cognitive and social deficits in NDDs (Rubenstein and Merzenich, 2003). Many NDDs also have comorbidity for epileptic seizures, indicating dysregulation of inhibitory neural control particularly during early developmental stages (Tuchman and Rapin, 2002). For Fragile X syndrome, there is an increase in seizure incidence relative to the general population (Musumeci et al., 1999), a susceptibility to audiogenic seizures and to epileptiform brain slice activity in the Fmr1-KO mouse (Chuang et al., 2005; Musumeci et al., 2000). At the molecular level, downregulation of many GABA-A receptor subunits is also reported in the Fmr1-KO mouse (Adusei et al., 2010; D'Hulst et al., 2006). The action of GABA changes from a depolarising to a hyperpolarising effect upon maturation during a cortical critical period in the first few postnatal weeks in rodents; This transition is significantly delayed in the somatosensory cortex of the Fmr1-KO mouse and is correlated with higher expression of the neuronal chloride transporter, NKCC1, at the critical period closure at P10 (He et al., 2014). The transition of the driving force for GABA and thus its switch to hyperpolarising actions is also altered in CA3 hippocampal neurons of Fmr1-KO mice, with a transient difference in driving force occurring at birth then reappearing during the second postnatal week and remaining even up to P30 (Tyzio et al., 2014). Thus, the alteration in GABAergic synaptic transmission and inhibitory balance in the brain in NDDs could arise from altered maturation of phenotypes within known critical periods requiring proper GABAergic regulation in the hippocampus and sensory cortex.

An alternative explanation to link critical periods to developmental phenotypic impairments in NDDs is that the spatio-temporal NDD gene expression itself could misregulate the mechanism underlying the phenotype within a known critical period. In this sense, the expression of the gene and corresponding level of protein shows a developmentally-regulated profile that determines the synaptic phenotype. Many NDD genes such as Fmr1, Ube3A, NF1 and Shank 3 are regulated in striking spatial and temporal profiles across the brain during neurotypical development, including in subcortical regions ((Kroon et al., 2013, Allen Institute for Brain Science, www.developingmouse.brain-map.org). Of particular interest, many genes linked to prominent NDDs show dynamic changes in expression in the subplate region of the developing mouse cortex, suggesting these targets could dysregulate cortical phenotypes at early developmental stages (Hoerder-Suabedissen et al., 2013). Identification of the spatial and temporal expression patterns for a gene causal for a specific NDD could then guide the search for early pre- or postnatal phenotypic impairments ('temporal' aspects) or guide towards subcortical expression for novel locations of impairments ('spatial' aspects). Given the pleiotropic nature of many known NDD genes such as Fmr1, which can regulate expression of over 800 different target mRNAs (Darnell et al., 2011), it is undoubtedly not such a simplistic matter to explain multiple cellular and behavioural phenotypes by the change of a single gene product alone but rather a cohort of altered proteins. The original NDD gene impairment though may be the trigger for such a complex process causing the initial onset of a developmental delay during a critical period followed by cascade of knock-on effects mediated via directly-regulated targets of the NDD gene itself.

2.3. Pharmacological and genetic rescue strategies at restricted developmental stages

In recent years, phenotypic impairments have been corrected by pharmacological or genetic rescue strategies in adulthood in different mouse models for NDDs including Down syndrome (Fernandez et al., 2007), tuberous sclerosis (Ehninger et al., 2008) and Fragile X syndrome (Michalon et al., 2012). Although many phenotypes can be corrected in the corresponding mouse models, the vast majority of studies report partial rescue of selected impairments and some deficits remain. Given that timing of pharmaceutical treatment could be key to the efficiency of correcting impairments, focus is now turning to early intervention in these mouse models. For Fragile X syndrome, early pharmacological rescue in Fmr1-KO mouse pups is more efficient in correcting spine morphology changes than a pharmacological challenge in adult mice (Su et al., 2011). In the TS65Dn mouse model for Down syndrome, a single dose of Sonic hedgehog pathway agonist SAG 1.1 in newborn mice is sufficient to rescue some impaired cerebellar and hippocampal

phenotypes and also behaviour in the adult TS65Dn mouse (Das et al., 2013). However, again this rescue was only partial and other cerebellar phenotypes remain uncorrected (Gutierrez-Castellanos et al., 2013). An alternative strategy to target the earliest critical periods in brain neurodevelopment is to treat antenatally in NDD models. Application of the NKCC1 antagonist, bumetanide, one day pre-delivery to pregnant Fmr1-Hz female mice and to VPA-pretreated pregnant rats restored CA3 pyramidal neuronal activity, hippocampal oscillations and altered pup vocalisations (Tyzio et al., 2014). In WT control mice, bumetanide caused a long-lasting disruption of excitatory synaptic transmission, developmental delay and impaired long-term sensorimotor gating when given during a restricted time window of development from E17 to P7 (Wang and Kriegstein, 2011). This outlines the timing of a critical period that could potentially be used for therapeutic intervention in comparable developmental stages in NDD models but also highlights the need for caution in long-term treatment applications during immature development.

The critical importance of timing in rescue of phenotypes in transgenic mice can be illustrated using a rodent model with in utero knockdown of the Dcx gene. Mutation of Dcx causes neuronal migration impairments resulting in subcortical heterotopia or double cortex syndrome (Bai et al., 2003). Timed reintroduction of the Dcx gene during early postnatal development reveals a partial phenotypic rescue but importantly, the rescue is only partially effective before postnatal day (P)5 and is ineffective if re-induced later in development (Manent et al., 2009). Thus there is a critical time-window during which phenotypic rescue, albeit partial, can occur. The existence of restricted time-windows for therapeutic rescue is also validated in the Drosophila fly model for Fragile X syndrome. Here, reintroduction of the FMRP homolog during a mid-phase of brain development was able to correct a dendritic phenotype during a period of circuit refinement. However, intervention at an early stage of circuit formation or in the adult fly was ineffective (Gatto and Broadie, 2009). Such timed intervention has not been shown yet for mammalian FMRP but it is vital to determine if the effectiveness of treatment is dependent upon known critical periods and specific developmental stages.

A critical aspect to the application of correcting neurodevelopmental impairments within the brain during known critical periods is that the brain exhibits multiple critical periods spread across differing brain regions, each of which has its specific underlying mechanism. Within a single region of the nervous system, the same developing neuronal network may undergo a succession of critical periods, supported by different neurotransmitter or ion channel-dependent processes. For example, retinal networks undergo a sequential series of synchronous network activation from perinatal development onwards that utilise first gap junction coupling, followed by nicotinic cholinergic receptor signalling and finally, a glutamatergic excitatory mechanism to mediate activity during later postnatal stages (reviewed in (Blankenship and Feller, 2010)). Within a regional circuit, there may also be synapse-specific impairments underlying an NDD. In the ILRAP1 mouse model for intellectual disability, thalamic projections onto principal neurons in the amygdala are significantly altered whereas similar projections upon neighbouring interneurons are unaffected at a similar timepoint (Houbaert et al., 2013). Finally, reintroduction strategies to re-express the affected protein in the brain an NDD are likely to need careful fine-tuning to re-establish the correct level of protein expression. The Shank gene family encodes for post-synaptic scaffolding proteins which are implicated in a number of synaptopathies, including Shank3 in Phelan-McDermid (22q13 deletion) syndrome (Grabrucker et al., 2011). Deletion of Shank3 in mice causes stereotypy, altered social interactions and spine dysmorphology (Peca et al., 2011). However, overexpression of Shank3 mimicking a patient duplication of Shank3, caused manic behaviours and epileptic seizures (Han et al., 2013). Illustrating a similar principle, differential expression of genes from 15q11–q13 chromosome region is also associated with cognitive impairments and autistic behaviours. Deletion of the region, which contains a cluster of imprinted genes, causes Angelman or Prader-Willi syndromes dependent upon lack of expression of the maternal or paternal allele (Nicholls and Knepper, 2001). However, duplication of region 15q11.2–13.1 commonly from the maternal chromosome, gives rise to 'dup15q syndrome' also leading to cognitive delay, sensory processing impairments and autistic behaviours (Chamberlain and Lalande, 2010). Thus, it is no straightforward matter to reintroduce a gene or alter specific protein expression in the brain in a location-specific, timing-restricted manner and thereby intervene in a complex pattern of developmental changes acting across overlapping regional critical periods.

2.4. Compensatory mechanisms at brain circuitry and behavioural levels in NDDs

For many syndromic NDD model studies, constitutional knockout mice with permanent genetic mutations are utilised yet many phenotypic impairments of neural and synaptic circuitry reported are transient (Kroon et al., 2013). One simple explanation for this could be that a form of compensation occurs within the brain circuitry to overcome the initial developmental delay or synaptic impairment. Such compensation mechanisms could operate through a homeostatic process to normalise or correct changes in neural activity, as shown during sensory manipulations in neocortex (Turrigiano and Nelson, 2004).

At the genetic level, there are currently around 450 genes associated with intellectual disability and many hundreds of candidate genes implicated in ASD (Betancur, 2011; Mitchell, 2011; State and Sestan, 2012; van Bokhoven, 2011). Many of these genes are interlinked via common cellular signalling pathways, and in ASDs are associated in large interacting networks commonly targeting synaptic function (Bill and Geschwind, 2009; Noh et al., 2013). Multiple de novo mutations in candidate genes occur as part of a synaptic interaction network linked to the disorder in some individuals with ASD whereas other ASD subjects have only a single gene mutation (Noh et al., 2013). While there are many penetrant mutations in genes such as Fmr1, Shank family members, TSC1/2 and neuroligins to name a few, it is not yet clear whether these candidates are dominant 'hub' genes with multiple interacting partners that could explain the phenotypic similarities in heterogeneous forms of ASD and ID in NDDs (Zoghbi and Bear, 2012). One potential highly simplistic explanation for the developmental delays commonly observed in many NDD phenotypes is that this delay arises due to the extra time needed for compensatory mechanisms within the network at a genetic level (Fig. 2). In a model system such as a knockout mouse for gene X (an NDD gene), the impairment would first arise coincident with the anticipated onset of gene X during neurotypical development (Fig. 2A and B). For the KO animal, an impairment such as a delayed phenotype would initially occur. However, given the drive for a system to reach its developmental 'checkpoints' or targets (Ben-Ari and Spitzer, 2010) the network would attempt to correct for this loss of gene X by alteration of other genes within the interacting network (Fig. 2C). The gene network may be able to compensate in part for loss of gene X via alternative signalling pathways or by duplicate genes possessing similar function but at a cost, namely that of time. This cost would manifest as a developmental delay in the function of the network or phenotype it supports and may translate to the developmental delays observed in NDD models during critical periods throughout the brain. Such a simplified pathway does not account for the multitude of consequential changes undoubtedly occurring in target genes and their products directly regulated by or interacting with

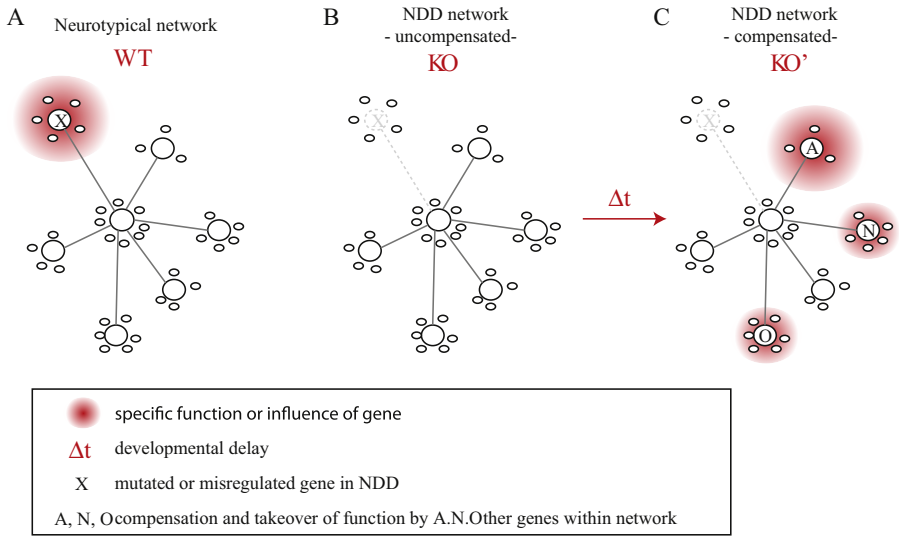

Fig. 2. Compensation within a genetic network may account for developmental delay. (A) In a simplified network of interacting genes with their local partners, gene X regulates a specific function within the network. (B) In a monogenic NDD model, a mutation of gene X effectively removes regulatory control of this function, giving rise to a phenotypic impairment. (C) With a delay (Δt), the KO network adjusts and other local genetic partners within the network support the missing function.

the original gene X. Rather, it aims to highlight the potential importance of compensatory network mechanisms which can contribute to the resultant phenotypic outcome in NDDs from intracellular to behavioural levels.

Compensation of function can also arise at systems and behavioural levels in people with NDDs (Johnson, 2012). fMRI data from children diagnosed with ASD revealed clear differences in how prefrontal cortex and temporal sulcus regions are activated relative to age-matched unaffected children. Interestingly, in this study, non-autistic siblings of the ASD subject group also showed different regional activity patterns relative to both ASD and neurotypical control subjects (Kaiser et al., 2010). Given that the unaffected siblings share 50% genetic material with their affected brother or sister and they carry a higher risk for developing ASD, their brain activation patterns may be a reflection of compensatory processing in individuals who are susceptible for an NDD but are not sufficiently affected to cross the threshold for diagnosis.

3. Summary

By using the concept of critical or sensitive periods to propose explanations for the onset and developmental progression of NDDs, this may act as a unifying concept for other key hypotheses in the neurodevelopmental field of ASD and ID. Firstly, an imbalance in the levels of excitation to inhibition in the brain is prominent for NDDs, particular ASD and IDs with ASD comorbidity (Rubenstein and Merzenich, 2003). Dysregulated excitatory and inhibitory ratios are observed in many human syndromes and their corresponding mouse models (Chattopadhyaya and Cristo, 2012). Secondly, hyperexcitability is a prominent feature across NDD models, which may link in part to an imbalanced E/I ratio, but emphasises the direct changes in elevated brain activity, connectivity and plasticity levels (Goncalves et al., 2013; Markram and Markram, 2010; Zoghbi and Bear, 2012). Finally, the third key hypothesis in the NDD field is that of altered connectivity in the brain on both local 'short-range' levels between neighbouring neurons in the same cortical layer or region and on long-range levels affecting axonal projections between distant brain regions (Belmonte et al., 2004; Courchesne et al., 2005; Just et al., 2004). Specifically for ASD, local connectivity is proposed to be excessive whereas long-range projections are postulated to be weaker due to decreased strength or fewer fibres (Belmonte et al., 2004; Just et al., 2004).

Placing the onset and progression of impairments underlying NDDs into a framework of known critical periods in brain development could provide explanations for the developmental aspects of specific phenotypes in these disorders. Both excitatory/inhibitory dysregulation, hyperexcitability and altered brain wiring hypotheses are still valid and can be incorporated into this concept. Furthermore, consideration of NDDs from a dysregulated critical period point-of-view may help to understand how similar phenotypic impairments arise from heterogeneous disorders of ASD and ID by focusing on spatio-temporal aspects of altered gene expression patterns in addition to the gene functions alone.

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