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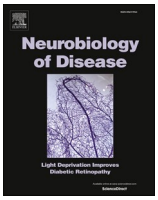

Synaptic genes and neurodevelopmental disorders: From molecular mechanisms to developmental strategies of behavioral testing

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ABSTRACT

Synaptopathies are a class of neurodevelopmental disorders caused by modification in genes coding for synaptic proteins. These proteins oversee the process of neurotransmission, mainly controlling the fusion and recycling of synaptic vesicles at the presynaptic terminal, the expression and localization of receptors at the postsynapse and the coupling between the pre- and the postsynaptic compartments. Murine models, with homozygous or heterozygous deletion for several synaptic genes or knock-in for specific pathogenic mutations, have been developed. They have proved to be extremely informative for understanding synaptic physiology, as well as for clarifying the patho-mechanisms leading to developmental delay, epilepsy and motor, cognitive and social impairments that are the most common clinical manifestations of neurodevelopmental disorders. However, the onset of these disorders emerges during infancy and adolescence while the behavioral phenotyping is often conducted in adult mice, missing important information about the impact of synaptic development and maturation on the manifestation of the behavioral phenotype. Here, we review the main achievements obtained by behavioral testing in murine models of synaptopathies and propose a battery of behavioral tests to improve classification, diagnosis and efficacy of potential therapeutic treatments. Our aim is to underlie the importance of studying behavioral development and better focusing on disease onset and phenotypes.

1. Introduction

Neurodevelopmental disorders (NDDs) are a broad class of brain diseases characterized by a spectrum of early clinical manifestations with developmental delay, cognitive/social impairment and seizures representing the most recurrent phenotypes. Main pathologies belonging to the NDD spectrum are intellectual disability (ID); Communication Disorders; Autism Spectrum Disorder (ASD); Attention-Deficit/Hyperactivity Disorder (ADHD); Developmental epilepsies, including early onset epileptic encephalopathy, and Neuro-developmental Motor Disorders. Next generation sequencing has allowed the identification of hundreds of genes responsible for NDDs, among which synaptic genes represent the most represented category. This evidence brought to use the term Synaptopathies, originally proposed in 2012 (Grant, 2012), to define this subclass of NDDs. Although a broader definition of Synaptopathies is also used for pathologies characterized by synaptic dysfunctions, here we use the term Synaptopathies as the class of diseases caused by modifications in synaptic genes. Synaptopathy genes encode for proteins acting at presynaptic and post-synaptic sites which regulate neuronal development and maintain excitation/inhibition balance through a variety of proposed mechanisms. Although many advances have been made on the definition of the pathophysiological mechanisms and the description of experimental models for the validation of novel therapeutic treatments, no cure is

Abbreviations: CNVs, copy number variations; CORT, cortistatin; KA, kainic acid; KO, knockout; KI, knock-in; ID, intellectual disability; NDDs, neurodevelopmental disorders; NLGN, Neuroligin; NRXN, Neurexins; PRRT2, proline-rich transmembrane protein; PTZ, pentylenetetrazole; STX-1, Syntaxin-1; STXBP1, Syntaxin binding protein 1; SYB2, VAMP2/synaptobrevin-2; SYP, Synaptophysin; SYT-1, Synaptotagmin-1; SV, synaptic vesicle; SWD, slow-wave discharge; VSCC, voltage-sensitive calcium channel; PSD, postsynapticdensity.

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currently available for this class of disorders. Many comprehensive reviews have been recently published to describe the different genes responsible for Synaptopathies, propose pathophysiological mechanisms and genotype/phenotype correlations and discuss on potential therapies (Bonnycastle et al., 2021; Cao and Tabuchi, 2017; John et al., 2021; Luo et al., 2018; Monteiro and Feng, 2017; Trobiani et al., 2020; Turner et al., 2021; Verhage and Sørensen, 2020).

In this scenario, beside emerging experimental models of human origin, such as induced pluripotent stem cell (iPS)-derived neurons and brain organoids (see, for recent reviews. Baldassari et al., 2020; Sterlini et al., 2020), animal models are necessary to test and validate potential therapeutic treatments. However, they need to be employed in the time window when developmental defects initiate and occur and with proper behavioral tests designed to address main features manifested in NDDs. An effective mouse model should incorporate face validity (i.e., strong analogies to the endophenotypes of the human syndrome), construct validity (i.e., the same biological dysfunction that causes the human disease, such as a gene mutation or anatomical abnormality) and predictive validity (the ability of a model to predict drug efficacy") (Willner, 1991; Nestler and Hyman, 2010; Silverman et al., 2020). No animal model will ever fully recapitulate a uniquely human disorder such as NDD. Validation of rodent models is based on a parallel identification of one or more of the distinctive clinical features of the NDD studied, through a set of selected behavioral tasks. Behavioral phenotyping can be addressed by targeting the main symptoms of the NDD analyzed, considering that additional behavioral tests are often necessary to provide complete information about the phenotypes, since these disorders commonly exhibit comorbidities or cognitive symptoms that potentially mask the disease core.

Over the recent years, a number of behavioral phenotyping assays for rodent NDD models have been developed to assess different aspects of motor, sensory, social and cognitive domains in adult animals (Wahlsten et al., 2003; Crawley, 2008; Gulinello et al., 2019). However, the onset of NDDs emerges during infancy and adolescence. Thus, even if the research in adult mice allows easy handling, assessing social interaction during mating, and evaluation of complex cognitive abilities, important information about the impact of synaptic development and maturation on the behavioral phenotype during development is often missing. In this context, behavioral studies conducted in the developmental time window that matches the onset of symptoms in humans may improve the validity of the mouse models and help in understanding the etiology of NDDs.

Here, we briefly summarize the molecular functions of a set of genes resulting in synaptopathies when mutated (Table 1 and supplementary file 1). They have been selected for their clinical relevance together with the availability of knockout (KO) or knock-in (KI) murine models (Table 1 and supplementary file 2). We then review the main achievements obtained by behavioral testing in these models and propose a strategy to further study behavioral development and better focus on disease onset and phenotypes with the aim to test potential therapeutic treatments.

2. Synaptic genes in NDDs and their modelling in mice

Synaptic function is regulated by a multiplicity of proteins that oversees the process of neurotransmission, mainly controlling the fusion and recycling of synaptic vesicles (SVs) at presynaptic terminals, the expression and localization of receptors at postsynaptic sites and the coupling between the pre- and the postsynaptic compartment (see for recent reviews: Chanaday et al., 2019; Groc and Choquet, 2020; Sauvola and Littleton, 2021; Südhof, 2021; Chater and Goda, 2022). This tight control guarantees the development of neuronal circuits and the fidelity and plasticity of signal communication in the brain. Complete loss of many of these proteins is incompatible with life, however copy number variations (CNVs) and clusters of missense and nonsense mutations, most of which occurring *de novo*, in synaptic genes are described in patients with NDDs. We here present a group of NDD synaptic genes, based on the availability of animal models to study their function and pathophysiology. In order to schematically describe their molecular function and correlation with the disease, we divide them into four categories depending on the synaptic function of the codified proteins (Table 1): 1) neuronal SNARE proteins and their interactors; 2) proteins that regulate trafficking within the terminal; 3) synaptic adhesion proteins; 4) synaptic scaffold proteins.

Table 1
List of synaptic genes mutated in NDDs and described in the text.

Gene	Chrom. (H)	Functional role	Main NDD clinical manifestation	Inheritance
VAMP2	17p13.1	SNARE protein	hypotonia, ASD, ID,E	AD
SNAP25	20p12.2	SNARE protein	hypotonia, ID, E	AD
STX1B	16p11.2	SNARE protein	E, ID; neuropsychiatric symptoms	AD
SYT1	12q21.2	SNARE binding protein/ Calcium sensor	hypotonia, ID, E	AD
STXBP1	9q34.11	SNARE binding protein	E or severe epileptic encephalopathy	AD, AR
SYP	Xp11.22-p11.23	SNARE binding protein	hypotonia, restless movements, E	X-linked (R)
PRRT2	16p11.2	SNARE binding protein	E, ID ataxia	AD, AR
DNM1	9q34.11	SV trafficking	ID, E, Developmental delay	AD
TBC1D24	16p13.3	SV trafficking	E or severe epileptic encephalopathy	AR
SYN1	Xp11.3-p11.23	SV trafficking	E, ID	X-linked (R)
SYN2	3p25.2	SV trafficking	E, ASD, schizophrenia	AD
NRXN1	2p16.3	Synaptic adhesion proteins	ASD, schizophrenia	AR
NLGN1	3q26.31	Synaptic adhesion proteins	ASD	AD
NLGN3	Xq13.1	Synaptic adhesion proteins	ASD	X-linked (R)
NLGN4X	Xp22.32-p22.31	Synaptic adhesion proteins	ID, ASD	X-linked (R)
SHANK2	11q13.3-q13.4	Synaptic scaffold proteins	ASD	AD
SHANK3	22q13.33	Synaptic scaffold proteins	developmental delay, schizophrenia	AD

3. Neuronal SNARE proteins and their interactors

Neuronal core SNARE proteins are the v-SNARE VAMP2 (also called Synaptobrevin-2, SYB-2), and the t-SNAREs, Syntaxin1 (STX-1) and SNAP25. Together with their regulators, SNARE proteins are responsible for the fusion of SVs with the plasma membrane at privileged sites where voltage sensitive Ca^{2+} channels (VSCC) transduce the action potential into an intra-terminal $Ca^{2}+$ influx that triggers exocytosis. Recent reviews nicely and comprehensively update on the current knowledge on SV fusion and its Ca^{2+}-dependent regulation (Brunger et al., 2019; Rizo, 2018; Sauvola and Littleton, 2021; Silva et al., 2021).

De novo heterozygous mutations in *VAMP2* have been described in patients with NDDs, having axial hypotonia, intellectual disability and autistic features as core symptoms, often associated with epilepsy (Salpietro et al., 2019; Simmons et al., 2020). Described mutations are loss of function and impair SVs fusion *in vitro* (Salpietro et al., 2019;

Simmons et al., 2020). Homozygous deletion (-/-) of *Vamp2* in mouse results in lethality at birth, while heterozygous (+/-) mice do not show gross behavioral deficits. However, the behavioral phenotype is limited to one study and the social behavior, representing the core symptom of the autistic features in patients, has not been investigated (Monteggia et al., 2019). Interestingly, thanks to high-throughput forward genetics screening an Ile102Asn substitution in VAMP2 has been identified in mouse as causative for sleep-wake alterations, a recurrent feature presents in NDDs (Banks et al., 2020).

Patients affected by hypothonia, intellectual disability and epilepsy as common manifestations, have been described to bear *de novo* heterozygous mutations in *SNAP25* (Hamdan et al., 2017; Hamdan et al., 2011a; Klöckner et al., 2021; Rohena et al., 2013; Shen et al., 2014). These mutations were considered as putative loss of function, as confirmed by functional evaluation (Jeans et al., 2007; Rebane et al., 2018). Distinct mouse lines for *Snap25* have been developed and, as for *Vamp2*$^{-/-}$, also *Snap25*$^{-/-}$ mice are not viable at birth. *Snap25*$^{+/-}$ animals are viable, fertile and informative on the behavioral phenotype, since they show deficit in sociability, social recognition, object recognition and hyperactivity together with epileptiform activity. In particular, heterozygous *Snap25*$^{+/-}$ mice displayed frequent spikes of high amplitude without spontaneous seizures but with an increased susceptibility to kainic acid (KA)-induced seizures (Corradini et al., 2014). The same behavioral and EEG profiles were observed in juvenile *Snap25*$^{+/-}$ mice (6-weeks old) and both deficits were effectively rescued by the antiepileptic drug valproate (Braida et al., 2015; Corradini et al., 2014). Mutant animals with a single amino acid substitution at the phosphorylation site Ser^{187} in SNAP25 display spontaneous seizures at around 3 weeks after birth, strong anxiety-like behaviors and cognitive dysfunction in adulthood, showing the physiological importance of SNAP25 post-translational modifications (Kataoka et al., 2011; Watanabe et al., 2015). Epileptogenesis was studied in these mutant mice and EEG recorded in young mice (P19) showed frequent spontaneous burst of spikes and slow-wave discharges (SWD) (Watanabe et al., 2015). Moreover, since SNAP25 exists in two developmentally regulated "a" and "b" isoforms, mutant mouse lines were generated. *Snap25b*$^{+/-}$ mice showed cognitive deficits and increased anxiety-like behavior already present in young animals at 1 month of age (Irfan et al., 2019; Johansson et al., 2008). The role of SNAP25b in behavior was also studied in a mouse bearing a missense mutation in a highly conserved codon (*Snap25Bdr* mouse). This mutant displays an ataxic phenotype with deficits in sensory motor gating, without alteration in anxiety and social behaviors (Jeans et al., 2007). To understand the exquisite role of SNAP25 in excitatory neurons, a conditional KO mice with specific loss of SNAP25 (*CaMKII-Snap25*) in forebrain glutamatergic neuron have been generated. They show a hyperactive and anxious profile together with stereotyped behaviors, social and cognitive deficits (Yang et al., 2017). As VAMP2, SNAP25 plays a role in the regulation of sleep/wake cycle as observed in mice with SNAP25 silenced in the layer V of the cortex that displayed increased wakefulness and reduced rebound of electroencephalographic slow-wave activity after sleep deprivation (Krone et al., 2021). Behavioral observations are in line with patient phenotypes and all models display cognitive deficits and either spontaneous epilepsy or increased epilepsy susceptibility. The emergence of motor alterations, such as ataxia or hyperactivity, was dependent on the specific mouse line. It is worth noting the presence of anxiety-like behaviors in all mice tested. However, an influence of anxiety on the motor performances cannot be excluded.

The other neuronal t-SNARE, STX-1 and in particular its B (STX1B) isoform was described to be mutated in several patients bearing heterozygous mutations with various degrees of seizures with motor and cognitive impairment. The *STX1B* associated pathology is very broad ranging from febrile and afebrile seizures with a benign course to intractable seizures with developmental regression and neuropsychiatric symptoms (Schubert et al., 2014; Wolking et al., 2019). Functional studies in zebrafish and mouse neurons indicate *STX1B* haploinsufficiency as pathogenetic mechanism, although a *de novo* V216E mutation identified in patients with severe epileptic encephalopathy and which increases SVs release probability *in vitro,* suggest that *STX1B* gain of function mutations could also occur (Schubert et al., 2014; Vardar et al., 2020). Studies in mice argue for a prominent effect of the loss of function on GABAergic neurotransmission with consequent hyperexcitability, as observed in *Stx1b*+/- mouse pups and adults that display susceptibility to seizures induced by hyperthermia and pentylenetetrazole (PTZ), respectively (Mishima et al., 2021). In line with other presynaptic models, the *Stx1b*$^{-/-}$ full KO mouse is neonatally lethal (Wu et al., 2015).

The Ca^{2+}-sensor for synchronous neurotransmitter release, Synaptotagmin-1 (SYT-1), binds to the SNARE complex and triggers SV fusion upon Ca^{2+} entrance via VSCCs (Geppert et al., 1994; Xu et al., 2007). *De novo* heterozygous *SYT1* missense mutations in patients with NDD have been described (Baker et al., 2018). When modeled *in vitro*, the various pathogenic variants affect protein expression, localization or function of SYT-1, suggesting either haploinsufficiency or loss of function as prominent pathogenic mechanism (Baker et al., 2018). *Syt1*$^{-/-}$ mice die 48 hrs after birth while, the *Syt1*$^{+/-}$ mouse is viable, but has not been behaviorally investigated (Geppert et al., 1994). However, the homozygous *Syt1* mouse bearing a mutation (SYT1R233Q) reducing its affinity for Ca^{2+}, revealed no overt deficits when studied for anxiety, motor coordination and locomotion, spatial and fear memories (Powell et al., 2004).

Among SNARE-interacting proteins, Syntaxin binding protein 1 (STXBP1/Munc18) is known to regulate docking, priming and fusion of SVs and to be fundamental for Ca^{2+}-evoked exocytosis (Toonen et al., 2006; Verhage et al., 2000). *De novo* heterozygous mutations in *STXBP1* are one of the most common genetic cause of NDDs with epilepsy. More than 250 patients have been described with severe forms of NDD with epilepsy as Ohtahara syndromes, West syndrome, Lennox Gasteau syndrome, Dravet syndrome and Rett syndorme (Saitsu et al., 2008; Otsuka et al., 2010; Milh et al., 2011; Carvill et al., 2014; Olson et al., 2015; Romaniello et al., 2015; Stamberger et al., 2016; Mastrangelo, 2017; Kovačević et al., 2018a). Additional patients are described with a milder NDD phenotype characterized by intellectual disability and seizures (Hamdan et al., 2011b; Hamdan et al., 2009). Many of the described pathogenic variants cause protein instability, leading to haploinsufficiency with impairment of synaptic transmission. Recently, a couple of patients with Lennox-Gastaut syndrome were also described with homozygous mutation (c.1336C>T; p.L446F) and a putative gain of function mechanism (Lammertse et al., 2020). The *Stxbp1*$^{-/-}$ mouse is embryonic lethal and all behavioral studies were conducted in the different heterozygous mice (*Stxbp1*+/-, *Stxbp1a, Stxbp1b)*, resulting in a similar behavioral profile. Video-EEG recordings revealed myoclonic jumps and jerks with cortical hyperexcitabilty together with several epileptiform activities, such as SWD, that respond to levetiracetam (Chen et al., 2020; Kovačević et al., 2018b). Together with the epileptic susceptibility, these mice also display motor defects resembling dystonia starting from 4 weeks of age, stereotyped behaviors, an aggressive profile and deficits in several cognitive tasks (Chen et al., 2020; Orock et al., 2018). The fear conditioning deficits were present also in conditional animals with *Stx1b* specifically deleted in dorsal telencephalic excitatory neurons (*Emx-Stx1b* mice), while a tendency was present in mice with *Stxbp1* specifically deleted in inhibitory neurons (SLC32A1-Stxbp1 mice), suggesting that the synaptic transmission alterations in the dorsal telencephalic and subcortical neurons are responsible for learning deficits (Miyamoto et al., 2017).

Synaptophysin (SYP) is an abundant protein in SVs and interacts with the v-SNARE SYB2. SYP function has been elusive for a long time, but the current experimental evidence suggests that it regulates SYB2 retrieval from the plasma membrane after fusion and the back-trafficking of SYB2 at the SV membrane (for a recent review, see Cousin, 2021). SYP is encoded by the *SYP* gene located in the X-chromosome and several nonsense and missense mutations in *SYP* are

described in X-linked intellectual disability with epilepsy and frontotemporal dementia (Harper et al., 2017a; Prota et al., 2021; Tarpey et al., 2009). When modeled in murine neurons, pathogenic variants result in defective targeting of SYB2 to SVs as described in *Syp* KO neurons (Harper et al., 2017b). Nonsense-mediated decay and complete loss of expression is described for several mutations (Tarpey et al., 2009) and *Syp*$^{-/-}$ mice represent a useful model to study NDD diseases; however, to our knowledge, their behavioral phenotype has not been characterized in detail, and only deficits in object recognition and spatial learning have been observed in adult mice (Schmitt et al., 2009).

The proline rich transmembrane protein 2 (PRRT2) associates with SNAP25 and SYT and participates in the regulation of synchronous neurotransmission (Stelzl et al., 2005; Lee et al., 2012; Li et al., 2015; Valente et al., 2016). Other roles for PRRT2 have been described recently, as its interaction with voltage dependent ion channels and transporters that play a key role in the regulation of neuronal intrinsic excitability (Fruscione et al., 2018; Ferrante et al., 2021; Sterlini et al., 2021). Mutations in the *PRRT2* gene have been identified as the main cause of a spectrum of diseases including paroxysmal kinesigenic dyskinesia of infancy, benign familial infantile epilepsy and complex NDD with epilepsy, prolonged ataxia and ID (Chen et al., 2011; Wang et al., 2011a; Labate et al., 2012; Lee et al., 2012; Méneret et al., 2012; Liu et al., 2013; Huang et al., 2015; Lindy et al., 2018). Most mutations are heterozygous and cause mRNA or protein degradation indicating a loss-of-function pathogenetic mechanism. The few homozygous or compound heterozygous mutations are associated with more severe phenotypes (Lee et al., 2012; Labate et al., 2012; Liu et al., 2013; Fruscione et al., 2018). When modelled in human neurons, pathogenic mutations result in hyperexcitability (Fruscione et al., 2018). The *Prrt2*$^{-/-}$ mouse is available and recapitulates many of the phenotypic features of the human *PRRT2*-linked disorders. The *Prrt2-/-* mouse shows abnormal motor behaviors starting from the first postnatal days and a motor/epileptic phenotype in response to environmental stimuli or PTZ in association with slight deficits in spatial memory (Michetti et al., 2017b; Robertson et al., 2019; Tan et al., 2018; Fay et al., 2021). A *Prrt2* mutant with a nonsense mutation (*Prrt2*-Stop) and various conditional *Prrt2* KO animals have been generated. They show spontaneous dyskinesia attacks under natural conditions, but also attacks induced by hyperthermia, kindling or PTZ induction. In addition, specific deletion of *Prrt2* in cerebellar granule cells is sufficient to induce the dyskinetic phenotype in mice, while the ablation of *Prrt2* in the forebrain is apparently ineffective (Tan et al., 2018).

4. Proteins that regulate trafficking within the terminal

SV cycling at presynaptic sites is the most regulated membrane trafficking process in cells. Upon exocytosis, SVs are promptly retrieved from the plasma membrane with different mechanisms depending on the kind of stimulus that elicited the exocytosis process; both clathrin-dependent and independent endocytosis operate at nerve terminals (Chanaday et al., 2019; Gan and Watanabe, 2018; Lou, 2018; Maritzen and Haucke, 2018). Dynamin1 is the specific GTPase expressed at presynaptic terminals that allows the pinch off of the piece of membrane that has been incorporated in the presynaptic membrane during exocytosis, no matter which mechanism of endocytosis is used (Chanaday et al., 2019; Ferguson and De Camilli, 2012). *De novo* heterozygous mutations in the gene coding for Dynamin 1 (*DNM1*) have been described in patients with clinically severe NDD with developmental delay, ID and seizures (Allen et al., 2016; Appenzeller et al., 2014; Epi4 Consortium E et al., 2013; Deng et al., 2016; Nakashima et al., 2016; Von Spiczak et al., 2017). Mutations are both missense and nonsense and they are localized mainly in the GTPase or the middle domain of the protein, with a predicted loss of function phenotype (Li et al., 2019). Additional *de novo* heterozygous mutations associated with a milder phenotype and not presenting epileptic seizures were also described in the PH domain (Brereton et al., 2018). In the mouse, a spontaneous missense mutation occurs in a highly conserved alternate exon of *Dnm1*, causing ataxia from P12 and severe lethal seizures before weaning in homozygous *Dnm1 fitful* mice. Heterozygous *fitful* mice showed partial and generalized tonic-clonic seizures upon routine handling at 2/3 months of age (Boumil et al., 2010). However, they have a normal lifespan, slight motor deficits in pups and a modest reduction in seizure threshold in response to repeated electrical stimuli (Boumil et al., 2010). Evaluation of conditional animals with *fitful* mutation in inhibitory or excitatory neurons suggest that the homozygous deletion is sufficient to cause early-onset epilepsy and premature death in almost all classes of inhibitory neurons tested (GAD, PV, SST and Dlx5/6) except for cortistatin (CORT) interneurons. The lethality in CORT conditional mice is around 47% at 6 months of age. Different EEG abnormalities were recorded in a low percentage of conditional mice that do not suffer from lethality. *PV-Dnm1fitful* mice presented SWDs during immobility periods, while *SST-Dnm1fitful* displayed high amplitude poly-spike and slow-spike waves. The homozygous deletion in excitatory neurons (*Emx-Dnm1fitful*) resulted in later onset non-lethal seizures (2-5 months) together with stereotyped behaviors, hyperactivity and an anxious phenotype (Asinof et al., 2015). The analysis of the DNM1 isoforms in *Dnm1a* and *Dnm1b fitful* mice showed that both strains had a normal lifespan without spontaneous seizures. However, *Dnm1a* mice have a lowered seizure threshold in comparison to both wild type and *Dnm1b fitful mice* and show episodes of epileptiform spikes (Asinof et al., 2016). While *DNM1b* is the predominantly expressed isoform during the gestational age, *DNM1a* predominates in the adult phase with its expression peaking around P14. A recent paper on AAV-mediated RNAi-gene therapy shows that the intracerebroventricular viral injection of a *Dnm1*-targeted therapeutic microRNA (miDnm1a) in *fitful* pups is able to suppress the ataxic behavior and improve motor and seizure behaviors (Aimiuwu et al., 2020). In line with *fitful* mice, targeted KO animals for the *Dnm1* gene die in the first two postnatal weeks; however, both *Dnm1*$^{-/-}$ and *Dnm1*$^{+/-}$ do not show overt epileptic phenotype (Ferguson et al., 2007). Unfortunately, mouse lines for Dynamin 1 have not been yet investigated for social and cognitive abilities.

Once endocytosed, SVs undergo cycling in the terminal to replenish the recycling pool of vesicle. TBC1D24 protein has been reported to regulate the SV fate at presynaptic terminals acting on the small GTPases Rab35 and Arf6 (Fernandes et al., 2014; Finelli et al., 2019; Tagliatti et al., 2016; Uytterhoeven et al., 2011). TBC1D24 also orchestrates neurite development and spine density through the inhibition of Arf6 (Falace et al., 2014; Lin et al., 2020). Various homozygous and compound heterozygous mutations either nonsense, truncating or missense in *TBC1D24* have been described in different form of NDD ranging from mild infantile epilepsy to severe epileptic encephalopathy (Balestrini et al., 2016) and a rare syndrome with deafness, onychodystrophy, osteodystrophy, mental retardation and seizures (DOORS) (Campeau et al., 2014). Pathogenic variants are scattered along the entire sequence and have been reported to impair binding with Arf6 (Falace et al., 2010; Milh et al., 2013), SV cycling (Muona et al., 2015; Fischer et al., 2016; Vissers et al., 2017; Lüthy et al., 2019), and to result in protein degradation (Lin et al., 2020), suggesting a loss of function phenotype. Although no clear phenotype/genotype correlation is evident, truncating mutations are often associated with the most severe manifestations and early death (Balestrini et al., 2016; Guven and Tolun, 2013). Human neurons derived from a patient with severe epileptic encephalopathy bearing p.Asp11Gly homozygous mutation showed defective neurite arborization (Stražišar et al., 2015; Aprile et al., 2019; Balestrini et al., 2016), but the synaptic phenotype has not been investigated yet. Distinct mouse lines for *TBC1D24* have been developed but the *Tbc1d24-/-* mouse is not available because of its embryonic lethality. Heterozygous mice are viable and fertile and show no alterations in the behavioral assessment of posture and locomotor activity in pups (Finelli et al., 2019). Homozygous mice for the human mutation S324Tfs*3 exhibit spontaneous tonic-clonic seizures starting from 2 weeks of age and die at 3 weeks. The epileptic phenotype is not present in

heterozygous *Tbc1d24*-S324tf*3 suggesting that the mutation is recessive as in reported patients (Balestrini et al., 2016; Tona et al., 2019). Adult mice with acute silencing of *Tbc1d24* in the hippocampus display impaired learning and memory in the fear conditioning test together with an anxious and hyperactive profile. Homozygous KI mice for the F251L mutation show spontaneous epilepsy and die at P21 (Lin et al., 2020). Other KI mice for *Tbc1d24* (H336Qfs*12/S324T*3) were recently reported to result in spontaneous seizures and early death, whereas homozygous KI mice expressing dominant or recessive mutations described in patients with deafness did not present detectable hearing impairment (Tona et al., 2019). Unfortunately, other behavioral domains have not been tested in the currently available *Tbc1d24* mice models. Thus, preclinical studies in animal models confirm a role for TBC1D24 in the establishment of epileptic phenotype and intellectual disability, although more studies are needed to characterize seizure insurgence and test potential rescue strategies.

The Synapsin protein family is known to regulate the distribution of SVs among distinct functional pools (ready releasable, recycling and resting pools, Alabi and Tsien, 2012; Pieribone et al., 1995) present in the terminals (Messa et al., 2010; Verstegen et al., 2014). Moreover, SYNs play additional post-docking roles at the terminal, differentially regulating synchronous and asynchronous neurotransmitter release (Baldelli et al., 2007; Medrihan et al., 2013, 2015) and are also involved in neuronal development by regulating membrane trafficking at the growth cone (Fornasiero et al., 2010). Both truncating and missense recessive homozygous mutations in the *SYN1* gene have been associated with NDDs with or without epilepsy (Fassio et al., 2011; Garcia et al., 2004; Guarnieri et al., 2018). Additional patients with ASD with or without concurrent epileptic phenotype, have been described with *de novo* heterozygous mutation in *SYN2* gene (Corradi et al., 2014). Both *SYN1* and *SYN2* pathogenic variants, when modelled in murine neurons, result in a loss of function phenotype with defective ready releasable pool and impaired SV cycling (Corradi et al., 2014; Fassio et al., 2011). Homozygous KO mice for *Syn1* and *Syn2* or double KO for both genes, display seizures evoked by a simple cage change starting from 2-3 months of age (Etholm et al., 2013; Etholm et al., 2012; Etholm et al., 2011). Double *Syn1* and *Syn2* homozygous KO mice show that only some cortical EEG recordings revealed epileptic regular discharges, but without clear behavioral seizure correlates. Thus, this suggests that hyperexcitability in other brain regions causes the epileptic phenotype, as confirmed by ex-vivo electrophysiological studies in hippocampal slices of $Syn2^{-/-}$ and triple-KO (TKO) mice (Etholm et al., 2011; Farisello et al., 2013; Medrihan et al., 2015; Medrihan et al., 2013; Toader et al., 2013). Thanks to the availability of homozygous mice, the behavioral phenotype has been extensively characterized. The cognitive profile is compromised in both $Syn1^{-/-}$ and $Syn2^{-/-}$ mice, even if cognitive deficits appear only in adult and old mice (Corradi et al., 2008). In addition, homozygous mice display deficits in social behavior starting from the first postnatal weeks and persisting in adulthood (Greco et al., 2013; Michetti et al., 2017a). $Syn2^{-/-}$ mice show the most severe autistic-like phenotype with an almost total absence of vocalizations in the adulthood together with repetitive behaviors (Greco et al., 2013; Michetti et al., 2017b). Interestingly, a role for SYN2 (isoform b) in the regulation of social hierarchy has been proposed showing that it is a marker of submissive behaviors and its reduction led to social dominance (Ma et al., 2020; Nesher et al., 2015).

5. Synaptic adhesion proteins

The tight coupling between the presynaptic terminal and the postsynaptic site is established, maintained and regulated by synaptic adhesion proteins. Neurexins (NRXNs) and Neuroligins (NLGNs) are the best characterized synaptic adhesion protein families, although many other adhesion molecules are shown to act at synapses. They interact transynaptically and, due to their differential expression and interaction, they specify synaptic subtypes and regulate inhibitory and/or excitatory neurotransmission. The multiplicity and complexity of synaptic adhesion molecules is overwhelming and point to this class of proteins as main actuators of synaptic diversity and target-specificity in the brain (Südhof, 2021; Südhof, 2017; Südhof, 2008).

NRXNs are a family of proteins expressed at the presynaptic site that interact with NLGNs and other postsynaptic adhesion molecules at the postsynaptic site playing an important role in synapse function and development through the functional coupling of VSCCs with the presynaptic machinery (Missler et al., 2003). In humans, there are three *NRXN* genes (*NRXN1*, *NRXN2* and *NRXN3*) each encoding for two major isoforms, a longer α-NRXN and a shorter β-NRXN (Ushkaryov et al., 1992; Tabuchi and Südhof, 2002). CNVs in *NRXN* genes are associated with diverse NDDs, especially schizophrenia, autism, ID, epilepsy and Tourette syndrome (Kim et al., 2008; Zahir et al., 2008; Gauthier et al., 2011; Duong et al., 2012; for a recent review, see Tromp et al., 2021). Most of the variations are described in *NRXN1* gene and result in heterozygous *NRXN1* deletion. When modelled in human neurons, the heterozygous *NRXN1* deletion results in synaptic impairment whereas no functional analyses are available from cultured neurons from hetero- or homozygous *Nrxn1α* KO mice (Pak et al., 2021; Pak et al., 2015). In addition, a gain of function mutation in a patient with severe intellectual disability and epilepsy has been shown to enhance the interaction of NRXN with the postsynaptic LMRR2, thus increasing excitatory neurotransmission in murine models (Restrepo et al., 2019). Mouse mutants for *Nrxn1* were generated on either a pure C57BL/6J or mixed (129X1/SvJ x 129S1/Sv) F1 and C57BL/6 background with conflicting data (Etherton et al., 2009; Grayton et al., 2013). An anxious profile was present only in $Nrxn1a^{-/-}$ on C57BL/6J background (Grayton et al., 2013), while repetitive behaviors and deficits in sensory motor gating were observed only in $Nrxn1a^{-/-}$ with hybrid background (Etherton et al., 2009). No major cognitive deficits were observed in both homozygous mice, while conflicting data were observed for the social behavior. The detailed characterization of the social behavior reveals the absence of important deficits in $Nrxn1a^{-/-}$ mixed background, while, social communication deficits and aggressive behavior were reported in a recent paper studying the developmental trajectory of $Nrxn1a^{-/-}$ mutants on a pure C57BL/6J background (Armstrong et al., 2020; Etherton et al., 2009). Pups lacking NRXN1a show delays in reaching certain developmental milestones and emit a reduced number of USVs indicating an alteration in the socio-communicative domain that persists in juvenile and adult mice (Armstrong et al., 2020; Grayton et al., 2013). These studies used different behavioral tests to evaluate the social behavior and this could potentially explain the conflicting results. The transgenic *Nrxn1b* mouse, in which *Nrxn1b* is expressed in postnatal neurons, display a selective impairment during the late postnatal stages recapitulating an autistic-like behavioral profile with deficits in social abilities and repetitive behaviors. This phenotype can be restored by removing the mutant protein in old mice, suggesting that therapeutic interventions to rescue NRXN function could be effective not only during infancy (Rabaneda et al., 2014).

NLGNs, the main postsynaptic counterpart for NRXNs, are encoded by 5 different genes in humans: *NLGN1*, *2*, *3*, *4X*, and *4Y* or *5*. NLGNs are differentially expressed at excitatory *versus* inhibitory synapses with NLGN1 and 4X specific for excitatory synapses, NLGN2 specific for inhibitory synapses and only NLGN 3 expressed at both synapse types. NLGNs act as dimers and bind both α- and β-NXNRs to form and shape synaptic connections (Lisé and El-Husseini, 2006). Missense and truncating hemizygous or heterozygous mutations in the *NLGN* genes have been associated with ASD and ID and mainly reside in the extracellular domain (Jamain et al., 2003; Laumonnier et al., 2004; Yan et al., 2005; Jiang et al., 2013; Redin et al., 2014; Geisheker et al., 2017; Nakanishi et al., 2017; Parente et al., 2017; Quartier et al., 2019). When modelled *in vitro*, the pathogenic variants result in defective protein folding and trafficking to the plasma membrane or impaired interaction with presynaptic partners (De Jaco et al., 2010; Marro et al., 2019; Nguyen et al., 2020). This evidence points to a loss of function phenotype associated

with ER retention and unfolded protein response as additional pathogenic mechanisms (Ulbrich et al., 2016). A gain of function mutation was also described in *NLGN3* with R451C mutation resulting in increased inhibitory transmission (Tabuchi et al., 2007). Conflicting data have been collected in mice bearing the homozygous R451C mutation. Some papers reported social deficits in adult animals, while another study reported a reduction in the vocal communication only in pups, together with slower righting reflex latencies and slight cognitive defects in adulthood (Chadman et al., 2008; Etherton et al., 2011; Tabuchi et al., 2007). In line with the KI model, *Nlgn3*$^{-/-}$ mice display socio-communicative deficits in the adult phase, in association with olfactory deficits that, interestingly, are also present in some ASD patients (Bennetto et al., 2007; Radyushkin et al., 2009). Recently, it has been shown that heterozygous mice bearing a *Nlgn3* mutation that impairs the NLGN3-NRXN interaction display increased sociability, while heterozygous mice where NLGN-PTP (protein tyrosine phosphatase γ, another interactor of NLGN3) is impaired display social defects and enhanced motor learning. Thus, these data suggest that a canonical and a non-canonical NLGN3 signaling compete and regulate social behavior (Yoshida et al., 2021). In general, a detailed behavioral characterization has been performed in all *Nlgn* mouse lines. *Nlgn1*$^{-/-}$ mice showed slight social deficits, increased repetitive stereotyped grooming and impaired spatial memory (Blundell et al., 2010). Homozygous animals carrying the human mutation P89L (*Nlgn1*P89L) display decreased social ability and aggression together with spatial memory deficits (Nakanishi et al., 2017). *Nlgn2*$^{-/-}$ mice display an anxious profile with motor alterations, stereotypies and social deficits that emerges in pups with a reduction in vocal communication (Babaev et al., 2016; Blundell et al., 2009; Hines et al., 2008; Wöhr et al., 2013). Homozygous mice bearing the human mutation R21H display anxiety, sensory motor gating and spatial memory defects (Chen et al., 2017), while conditional mice with selective deletion of *Nlgn2* in the prefrontal cortex exhibit cognitive deficits (Liang et al., 2015). *Nlgn4*$^{-/-}$ mice appeared deficient in all experimental settings selected to test their social competences, ranging from social interaction to social approach and social memory, including USVs emission (El-Kordi et al., 2013; Jamain et al., 2008). Interestingly, they did not display repetitive behaviors or impairments in some of the other autism-like symptoms, such as deficits in sensory systems or in learning and memory (Jamain et al., 2008). Altogether, these studies performed on different NLGN mutant lines suggest a primary role for NLGNs in the regulation of social behaviors. Studies on the cortical EEG profile in NLGN models display an altered power spectra profile that impacts on the regulation of sleep/wake states in *Nlgn1*$^{-/-}$, *Nlgn2*$^{-/-}$ and homozygous *Nlgn3 R451C* mice. These observations suggest a role for this gene family in the regulation of sleep/wake states, an interesting feature since sleep impairments are present in some patients with NDD, particularly in ASD (El Helou et al., 2013; Liu et al., 2017; Seok et al., 2018).

6. Synaptic scaffold proteins

At the postsynaptic site, neurotransmitter receptors are dynamically expressed and clustered at postsynaptic density (PSD), a complex meshwork of proteins that has been mainly characterized for excitatory synapses. SHANK-family proteins – encoded by three individual genes: *SHANK1*, *SHANK2* and *SHANK3*- are multi-domain scaffold proteins forming the PSD at excitatory synapses. SHANK proteins interact with many synaptic proteins, including NLGNs, glutamate receptor complexes, and the cytoskeleton, acting as a master scaffold in the PSD. The SHANK family seems to have a role in synaptic strength and dendritic spine maturation, as demonstrated by studies performed in *Shank1* and *Shank3* KO mice. Interestingly, overexpression of SHANK1 *in vitro* resulted in dendritic spine enlargement and the expression of SHANK3 was sufficient to induce dendritic spine formation neurons (Roussignol et al., 2005; Sala et al., 2001). Several studies found a correlation between homozygous *SHANK* deletion or mutations, with global developmental delay, hypotonia, absent or severely delayed language, autistic behaviors, and intellectual disability (Wilson et al., 2003; Durand et al., 2007; Moessner et al., 2007; Gauthier et al., 2009; Guo et al., 2018; Wang et al., 2020). At the behavioral level, *Shank1*$^{-/-}$ mice display increased anxiety-like behaviors, motor defects and, in mouse pups, socio-communicative deficits (Silverman et al., 2011; Sungur et al., 2015; Wöhr et al., 2011). They also show impaired fear conditioning memory, but enhanced spatial learning and memory (Hung et al., 2008). An anxious profile was also observed in *Shank2*$^{-/-}$ mice, associated with hyperactivity, impaired spatial memory and social deficits in both newborn and adult mice (Ey et al., 2013; Schmeisser et al., 2012; Won et al., 2012). In addition, distinct conditional mouse lines have been generated for SHANK2. Conditional KO mice for *Shank2* in excitatory (*CaMKII*) and inhibitory (*SLC32A1*) neurons display hyperactivity and social deficits. The *CamKII*-conditional mice show also an anxious profile, while the *SLC32A1*-conditional mice show repetitive self-grooming (Kim et al., 2018). In line, selective deletion of *Shank2* in parvalbumin neurons generates a slight hyperactivity and an enhanced self-grooming, together with a decreased susceptibility to seizures induced by PTZ (Lee et al., 2018). The deletion restricted to cerebellar Purkinje cells leads to anxious behaviors, motor impairment and stereotypies, but does not recapitulate the social deficits (Ha et al., 2016). SHANK3 undergoes complex transcriptional regulation producing different protein isoforms, each one containing a distinct combination of the five different protein-protein interaction domains differently affecting the synaptic functions. Thus, different mouse lines have been generated to study the contribution of each isoform on the behavioral phenotype. Animals with the complete deletion of the ankyrin-repeat domains of SHANK3 (*Shank3e4-9* mice) have been largely characterized, showing impaired learning and memory, motor defects together with repetitive behaviors and social deficits under both heterozygous and homozygous conditions (Bozdagi et al., 2010; Jaramillo et al., 2016; Wang et al., 2011b; Yang et al., 2012). Similar behavioral alterations with a stronger motor phenotype have been observed in pups and adult animals with homozygous deletion of the exon 4-22 (*Shanke34-22*) that generates the disruption of all three SHANK 3 isoforms (Wang et al., 2016). Instead, the insertion of a stop cassette in exon 13 is responsible for stereotypies and social defects in both homozygous and heterozygous *ShankE13* mice (Jaramillo et al., 2020; Jaramillo et al., 2017). Moreover, two mutant lines have been generated named *Shank3A*, where the Shank3α isoform was deleted, and *Shank3B*, where both SHANK3 isoforms were deleted (Peça et al., 2011). Only *Shank3B* mutants show ASD-like features, such as repetitive grooming and reduced social behaviors together with anxiety behaviors and deficits in learning and memory (Peça et al., 2011; Dhamne et al., 2017). Taken together, the data indicate that the SHANK gene family plays an important role in the regulation of various behavioral domains.

7. What behavioral phenotyping in mice tells us?

What do we learn from the behavioral characterization of the available models for synaptic NDDs? What is still to be studied for the understanding of the genotype-phenotype correlation necessary both for a more precise diagnosis and a correct employment of these models to test and validate novel therapeutic interventions? As described in the previous paragraphs, behavioral deficits analyzed in the available murine models show how alterations in presynaptic and postsynaptic proteins are causative for deficits in specific behavioral domains affected in NDDs. To summarize the behavioral studies and focus on what can be further asked on NDD pathophysiology with the use of these models, we identify 7 main behavioral domains most affected by NDDs. In particular: epileptic phenotype, motor abilities (including coordination and learning), stereotypies, hyperactivity, social ability (including interaction, recognition and aggression), cognition (including learning and memory tests to evaluate object, spatial and fear memory) and anxiety. Based on the behavioral data available, in Fig. 1 and supplementary file 2 we show which genes play a role in one or more behavioral domains

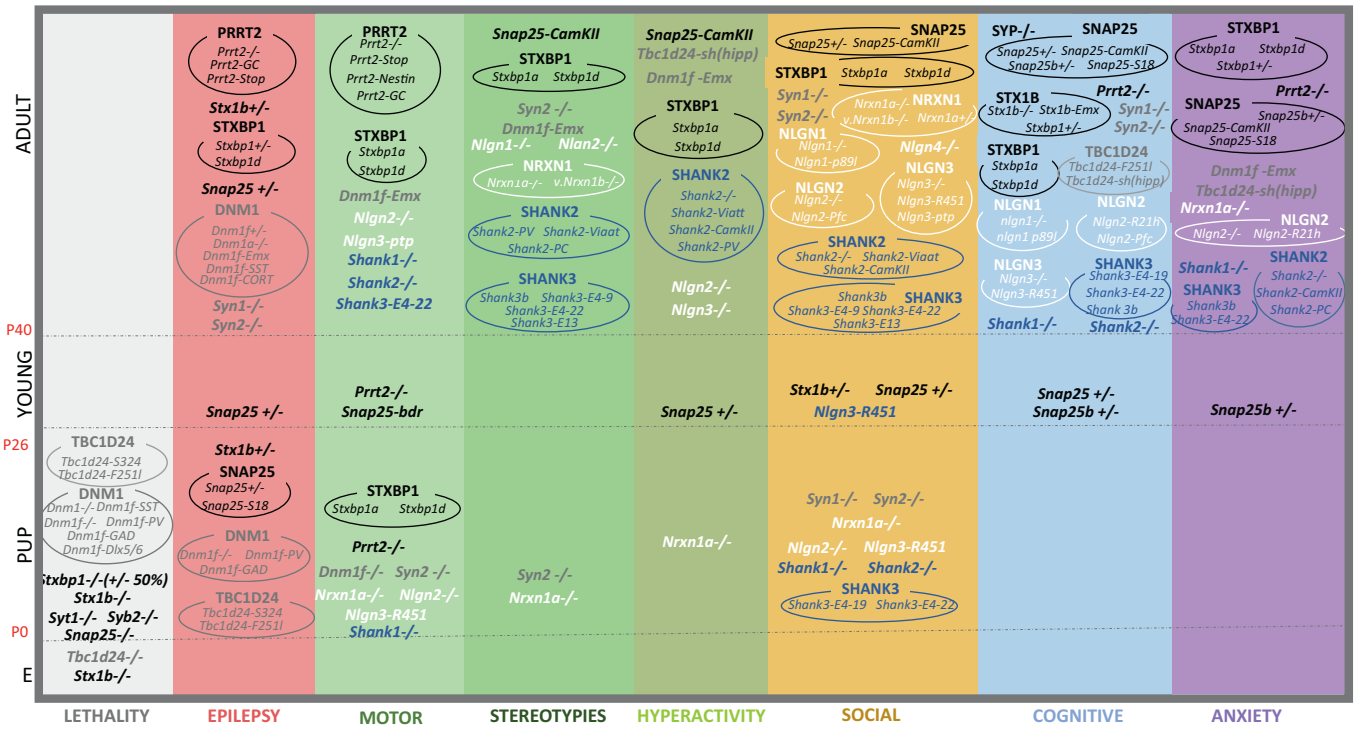

Fig. 1. Lethality and behavioral deficits observed in KO and KI mice for synaptic genes modelling NDDs. The four main stages of mouse's life considered comparable to human development are reported on the Y-axis: embryonal (E), pup (postnatal days P0-26), young (P26-P40), adult (from P40). Lethality and seven behavioral domains in which deficits were observed are reported on the X-axis. EPILEPSY: spontaneous or induced seizures evaluated for their latency, duration and/or severity measured through various seizure rating scales (e.g., Racine scale) and/or electro-encephalography (EEG) recordings. MOTOR: in young and adult mice, tremors and other locomotor abnormalities observed during the open field test and/or deficits in coordination and learning measured with the Rotarod test, Erasmus ladder and/or other specific tasks such as footprint, grip strength and/or vertical pole; in pup mice, delays in developmental milestones based on the Fox battery and/or tremors or other motor abnormalities recorded during spontaneous motor behavior. STEREOTYPIES: in young and adult mice, increased level of grooming behavior and/or marble burying in young and adult mice; in pup mice, high levels of pivoting, circling and/or face washing. HYPERACTIVE: increased level of locomotor activity measured during open field and/or spontaneous home cage activity in pup, young and adult mice. SOCIAL: in young and adult mice, social deficits recorded during social interaction and/or three-chamber test and aggression evaluated through male-male interaction and/or tube test; in pup mice, increased or decreased vocalization rate. COGNITION: learning and memory deficits evaluated by fear conditioning, passive/active avoidance, novel object recognition and/or maze tasks. ANXIETY: anxious profile observed through open field, elevated plus maze and/or light/dark test.

and the developmental stage of the evaluation.

The primary importance of presynaptic genes in brain development is supported by early lethality of homozygous knockout mice for SNARE genes (see for a recent review Verhage and Sørensen, 2020), being the full loss incompatible with life. In humans, most of the described patients bear de novo dominant mutations and show very severe clinical phenotype.

Only few homozygous animals for presynaptic genes reach the adult stage and are testable for their behavioral profile over their lifespan (pups, young, adults). Indeed, homozygous recessive mutations are described for these genes and KO models are a precious tool to study the pathophysiology of the related disorder.

The few homozygous mice for presynaptic genes that reach the adult stage, together with most of the heterozygous animals, display a brain hyperexcitability phenotype that appears as spontaneous or induced behavioral seizures (Michetti et al., 2017b; Tan et al., 2018; Mishima et al., 2021; Braida et al., 2015; Corradini et al., 2014; Watanabe et al., 2015; Boumil et al., 2010; Asinof et al., 2015; Asinof et al., 2016; Etholm et al., 2011, 2012, 2013). In line, EEG traces often associated with the analysis of seizure behaviors, show the presence of epileptiform activity represented by spiking activity (polispikes, interictal spikes or bilateral spikes) in many models for presynaptic genes, together with SWD that is another common feature among these models. These data recapitulate the epileptic phenotype present in most patients with mutations in these genes and demonstrate that murine models are an important tool to test and validate putative therapeutic treatments. On the contrary, at the postsynaptic site, only homozygous mutations in *Nlgn3* and *Shank3* are associated with epilepsy while, unexpectedly, *Shank*3B-/- and heterozygous *Nlgn*-R3451 display a decreased susceptibility to seizure (Dhamne et al., 2017; Hill-Yardin et al., 2015).

Looking at the motor system, mutations in different presynaptic genes associated with epilepsy are also associated with motor impairments and defective motor coordination and learning in the murine models. Despite this observation, the available data suggest that these genes differentially affect the thalamic-cortical pathway and, in turn, their motor/epileptic phenotype appears different. In the case of PRRT2, its expression is high in neurons of the lower hindbrain, particularly in the cerebellum, where an altered synaptic plasticity at the parallel fibers-Purkinje cells synapses was found in the *PRRT2* KO mouse (Michetti et al., 2017b). Thus, network instability in the cerebellar-thalamic-cortical pathway seems to drive the paroxysmal motor/epileptic phenotype, as confirmed by the study in conditional animals in which PRRT2 was selectively deleted in cerebellar granule cells (Tan et al., 2018). Differently, STXBP1, Dnm1 and Syn2 play an important role in brain development and formation of excitatory/inhibitory circuits, as confirmed by the lethality of *STXBP1* and *Dnm1* KO mice (for the viability *Syn2*KO mice compensatory effects could be due to the paralogs Syn1 and Syn3). The epileptic/motor phenotype in these models seems to involve the hippocampal-thalamic-cortical circuit causing a more severe epileptic phenotype (Toonen et al., 2006; Feliciano et al., 2013; Toader et al., 2013; Asinof et al., 2015; Medrihan et al., 2015; Patzke et al., 2015; Orock et al., 2018; Aimiuwu et al., 2020; Chen

et al., 2020)

On the other side, models for postsynaptic genes involved in ASD display repetitive behaviors, suggesting the presence of alterations in the cortico-striatal pathway, although relatively few studies investigated in details the brain circuit alterations underlying the stereotyped behaviors (Peça et al., 2011; Kim et al., 2016; Wilkes and Lewis, 2018). Collectively, murine models broadly recapitulate the clinical manifestations of the patients showing repetitive behaviors, a core symptom for ASD, and a variety of ataxic and hypotonic motor impairments that are also present in several patients bearing homozygous or heterozygous mutations in SNARE proteins. A couple of models for each class of genes analyzed report a hyperactive profile that is difficult to interpret. However, hyperactivity may also represent a secondary symptom resulting from the overt epileptic phenotype or anxiety behaviors.

Regarding social behavior, the most comprehensive studies made on postsynaptic gene models revealed a significant defect in the social tests, recapitulating human symptoms being social impairment the first clinical sign of ASD. However, it is important to note that the evaluation of social behavior is very limited in presynaptic models, despite social impairment is a common feature in the broad spectrum of NDD manifestations and therefore needs further investigations. It is worth to notice that there is not a unique circuit responsible for sensorimotor transformation of socially encoded information. Social behavior is contributed by the ability to: recognize different contexts; receive specific sensory cues; modulate in real time the internal states (resulting from past social experience); respond with behavioral output as result of a decision-making process. All these processes occur simultaneously between interacting individuals, thus forming a reciprocal feedback loop in which each behavioral output provides a sensory input to the other individual/s (Chen and Hong, 2018). In addition, the phases in social behaviors could be divided into detection phase, approach phase, investigation phase and action phase (see for a review Wei et al., 2021). This high level of complexity explains the difficulties in the identification of specific brain circuits for social interaction. However, recent literature is helping to elucidate the role played by specific brain regions and neural circuits involved in social interaction, also including brain circuits involved in non-social behavior such as olfactory, auditory and reward systems. In fact, the sensory system integration in mouse social interaction appear to start with the activation of olfactory neurons, and successively the signal is distributed to multiple regions including cortical amygdala, piriform and entorhinal cortexes (Wei et al., 2021). The key area for goal-directed approach is the *nucleus accumbens* together with its projections to the amygdala, an important area for the codification of emotion (Ferretti et al., 2019). The pathway for vocal communication remains poorly understood, although USVs also activate nucleus accumbens and basolateral amygdala (Parsana et al., 2012; Sadananda et al., 2008; Willuhn et al., 2014; Wei et al., 2021). The activation of these complex brain networks requires both glutamatergic and GABAergic neurotransmission (see for a review, Wei et al., 2021). Thus, it is not surprising that alterations in either pre- or post-synaptic genes easily shift the balance in these systems causing a wide spectrum of social abnormalities or, more generally, a wide spectrum of symptomatology affecting different behavioral domains. Being these genes widely expressed in the brain, it is difficult to hypothesize their involvement in shaping a single specific circuit, rather than a role in synaptic assemblies and dynamics across multiple neural systems. ASD, characterized by social deficits as first symptom, is largely considered a connectopathy, since its genetic variants are associated with cellular alterations linked to neuronal wiring and function resulting from aberrant development (Sestan and State, 2018; Zerbi et al., 2021). Based on fMRI analyses on 16 autism mouse models, 4 etiologically relevant connectivity subtypes have been identified characterized by under/over connectivity in specific brain regions. Across all clusters, independently of the directionality and extent of connectivity changes, the somatomotor, olfactory and cortical regions are most frequently implicated in the atypical connectivity associated with ASD symptoms (Zerbi et al., 2021). These studies, together with a careful behavioral screening, could help in the identification of etiologically relevant connectivity pathways affected by genetic mutations.

Cognition, an important domain affected in NDDs, has been assessed in the vast majority of pre- and post-synaptic models, overall demonstrating a primary role of synaptic genes in the regulation of cognitive abilities. However, although we have grouped all cognitive tasks, each behavioral test isolates specific processes involving different brain network/circuits and pathways. Thus, their representation in this context is useful for a general view of the behavioral domains regulated by each gene, but it is not sufficient for a serious discussion about the role of this gene in cognitive network functions. In addition, a variety of models show an anxious profile that is difficult to interpret. The investigation of anxiety is a fundamental aspect since its high levels can influence the behavioral performance in any other task.

All the behavioral profiles discussed above provide important information on the endpoint of NDD, since they have been mostly evaluated in adult animals. However, NDDs impact on the growth and development of the brain, leading to a deviation of motor, cognitive and social abilities in the early stage of life. Unfortunately, this deviation is not restricted to a single behavioral domain or circuit, but impacts different domains, circuits and pathways, often creating a domino effect on neuronal systems during development, thus generating a spectrum of symptoms in NDDs. A further complication is the epileptic phenotype present in many of the models, that potentially confounds when attempting to specifically evaluate other behavioral domains. In both human and mice, it is very difficult to dissect if a behavioral impairment is directly due to the mutation or secondary to other manifestations, such as epilepsy (Cross and Guerrini, 2013; Turner et al., 2021). Thus, despite the important information coming from adult mice, it is evident that few mouse lines have been tested in the early postnatal phase (Fig. 1). For the few models in which this piece of data is available, important information comes out. The study of social behavior in *Syn* mouse pups by recording of ultrasonic vocalizations (see next paragraph) shows that communication deficits are present in both *Syn1*$^{-/-}$ and *Syn2*$^{-/-}$ mice in the first two weeks of life, thus preceding the seizure onset (Michetti et al., 2017a). In *Syn2*$^{-/-}$ mice, recapitulating the symptoms of ASD, social deficits and repetitive behaviors are already present in pup mice, thus showing that ASD-like phenotype is not secondary to the epilepsy in this model (Michetti et al., 2017a). From the study of *Nrxn1a*$^{-/-}$ mouse, another valid model for ASD because of the reported deficits in adult social behaviors, authors show the presence of motor abnormalities and repetitive face washing in pups, but not in adult mice (Armstrong et al., 2020). In *Shank1*$^{-/-}$ mice, the social deficits are present exclusively in postnatal phase, but not in adulthood (Silverman et al., 2011; Sungur et al., 2015). These considerations suggest that the study of specific symptoms requires a precise time window for their observation and, consequently, that behavioral studies during ontogeny could be useful even when the adult behavior appears intact. Other mice modelling ASD have been tested in the early postnatal phase, but the majority of these studies are limited to the social behavior. The study in *Prrt2*$^{-/-}$ mouse, a model for motor paroxysm and epilepsy, show the presence of a peculiar “bouncing” behavior (short body jerks when the animal is placed with the four paws on the floor) together with backwalking (the animal performs at least backward two steps with all four paws) and classical tremors in pup mice (Michetti et al., 2017b). A comprehensive understanding of this behavior needs further studies, since it could be interpreted as a general motor impairment or as a feature of infantile epilepsy. The latter signature, present in many patients with *PRRT2* mutations, requires a careful analysis in clinical diagnosis. In the end, the study in *Dnm1f* mice shows the presence of an ataxic phenotype in association with epilepsy in *Dnm1f*$^{-/-}$ pups, but not in *Dnm1f*$^{+/-}$ mice that display only epilepsy in adulthood (Boumil et al., 2010). The evaluation of neonatal behaviors could be useful and informative also for all mutants with early lethality in first two/three weeks of life.

Today, most of the genetic models evaluated in this time window are relative to ASD, nevertheless all NDDs have early onset. What is lacking is the identification of early symptoms (hoping that at early stage the affected behavioral domains are limited) and, in turn, the identification of early brain circuit alterations. To summarize, the identification of early signs of NDD could help to identify: (i) the onset time window; (ii) the behavioral domains and brain circuits primarily affected without the confounding secondary symptoms that develop in a later stage; (iii) early potential treatments able to suppress or attenuate the onset of the principal symptoms of the disorder with the possibility to decrease all the associated secondary symptoms.

8. How to assess neurodevelopmental behaviors in preclinical models of NDDs?

Each neural system is differentially timed during development and behavioral studies during ontogeny are informative about the development of specific competence in their appropriate maturational stages. Neurobehavioral studies in the field of developmental psychobiology were originally investigated in rats, but since the 90s, they have been successfully adapted to the mouse for toxicology investigation, permitting valid measurements of behavioral profile in newborn mice (Bignami, 1996; Cuomo et al., 1996). These evaluations could appear less specific than those conducted in adult animals, however a battery of these tasks could be informative on sensory-motor, socio-emotional and cognitive development, working as predictors for the later deficits or bringing to light transient behavioral deficits. Nevertheless, some considerations are important when studying early behavioral development in mice.

First of all, we have to take in account that rodents have a compressed time window of development during which many neurodevelopmental processes appear concurrently, while in humans appear dispersed, especially during prenatal and postnatal phases (Sousa et al., 2017). There is also a temporal shift for some neurodevelopmental processes that in human appears in prenatal phase and in mouse in early post-natal phase (blood brain barrier 23-32 weeks human; pnd1/3 mouse; peak in brain growth sprut, gliogenesis and increasing axonal and dendritic density 36/40 weeks human; pnd7-10 mouse; for a review see Semple et al., 2013). Other important temporal shifts are: peak in synaptic density at 50% of adult levels, peak in myelination rate, neurotransmitter and receptor changes that appear at 2/3 years in human and pnd 20-21 in mouse; structural maturation of prefrontal cortex 4-11 years human and pnd 25-35 mouse; (Semple et al., 2013). Thus, it is clear that small brains require less time to shape and mature brain circuits as confirmed by comparative studies (Sousa et al., 2017). Another important factor is the evaluation of the gene expression that could be different from humans and mice with regard to spatial and regional organization (Johansson et al., 2008; Kudo et al., 2007).

In the end, we have to consider the physical differences and their effects on behavior. Pups are born after a short pregnancy (around 21 days) and appear in highly immature state with eyes and ears closed. They are able to crawl and attach to the nipple for suckling, but need the mother contact for thermoregulation (Branchi and Ricceri, 2002). Thus, it is crucial to check for potential confounders, as alterations of body temperature, body weight and general somatic growth when working with pups. All these physical parameters can influence the behavioral responses that we are measuring. Parental care is another relevant variable, influencing physical and behavioral development of the pups and can differ among litters based on previous experiences (Bailoo et al., 2014; Cohen-Salmon, 1987; Pedersen et al., 2011). Thus, it is necessary to use pups coming from different litters to avoid the influence of the maternal effect in determination of the behavioral phenotype. When possible, the use of litters containing all genotypes (pups can be marked with foot-tattoo from P1-2) represents an useful strategy to provide internal control of the experiments. The behavioral characterization at all life stages (pup, young and adult) permits the identification of early signs and the tracking of the evolving spectrum of symptoms. To evaluate the behaviors in juvenile mice, a modified version of the adult behavioral tasks could be employed, while to test pup mice a limited number of tasks are available (see Branchi and Ricceri, 2002; Eltokhi et al., 2020).

Today, the most used behavioral tasks are limited to a battery of reflexes for sensory-motor system maturation and ultrasonic vocalizations for social ability development. Here, we have collected the available behavioral tests for the study of pup mice (Fig. 2) and invite researchers to develop other useful and informative tools for investigations of the murine models at this stage.

9. Sensory and motor system

The evaluation of postnatal reflexes, an experimentally strategy initially developed for behavioral teratology experiments, is often used as a first screening of health when an animal model is created. Several reflex batteries exist and are all based on the Fox classification (Fox, 1965). Fox performed the first major investigation of reflex development in mice, defining five periods of neurological development: perinatal (birth to 3 days), neonatal (3-9 days), postnatal transition (9-15 days), pre-juvenile (15-26 days) and juvenile (26-40 days, sexual maturity). The duration of these periods could be considered arbitrary since some responses persist or are modified within a period. A fine analysis of reflexes conducted in early stages of postnatal life could be informative about the growth and the development of the sensory motor system. The batteries include the evaluation of physical landmarks (pinnae detection, eye opening, etc.), sensory motor reflexes (motor response to sensory stimuli such as sound click, visual placing, vibrissa touch, cliff avoidance, righting reflex etc..) and motor coordination (grasping, vertical screen test, bar holding etc.). In addition to reflexes, it is possible to investigate spontaneous motor behavior starting from the first day of life. The evaluation could be conducted in a small chamber, a sort of small open field apparatus, where pups are free to move. Different behaviors can be analyzed and the most studied are locomotion and repetitive behaviors such as pivoting, circling and face washing (see *Syn2*$^{-/-}$ and *Nrxn1a* pups (Armstrong et al., 2020; Michetti et al., 2017a). Moreover, a careful observation could detect peculiar motor behaviors, such as the motor paroxysms observed in *Prrt2*$^{-/-}$ pups (Michetti et al., 2017b). The combined analysis of reflexes and spontaneous behaviors offers important information about the development of the motor sensory system that often results affected in NDD.

10. Socio-emotional system

Ultrasonic vocalizations (USVs) in mouse pups are considered a reliable index of social motivation and consequently they are investigated to characterize the social behavior in pups (Sewell, 1968). Pups vocalize in response to separation from the lactating mother and littermates. Vocalizations are considered a sign of an aversive affective state eliciting maternal exploratory and retrieval behaviors (Knutson et al., 2002; Panksepp, 2003). Pups usually vocalize for a brief period after separation from the nest and rapidly habituate. The emission of USVs follows a clear strain-dependent ontogenetic profile, with a peak at P4 for FVB and at P6 for C57BL/6J and 129X1 and a progressive decrease around the second postnatal week (Elwood and Keeling, 1982; Hahn et al., 1998; Roubertoux et al., 1996; Scattoni et al., 2008). Any deviation from the ontogenetic profile could be interpreted as a deficit; thus, recordings at different postnatal days are necessary to be informative on the social development. In addition to the vocalization rates, it is possible to study the vocal repertoire through the classification of calls in different categories. This analysis adds important information about the vocal profile and the quality of the communication (Scattoni et al., 2011; Scattoni et al., 2008). Interestingly, it is possible to conduct the analysis of spontaneous motor behavior together with the experimental session dedicated to USV recording, thus applying a useful strategy in

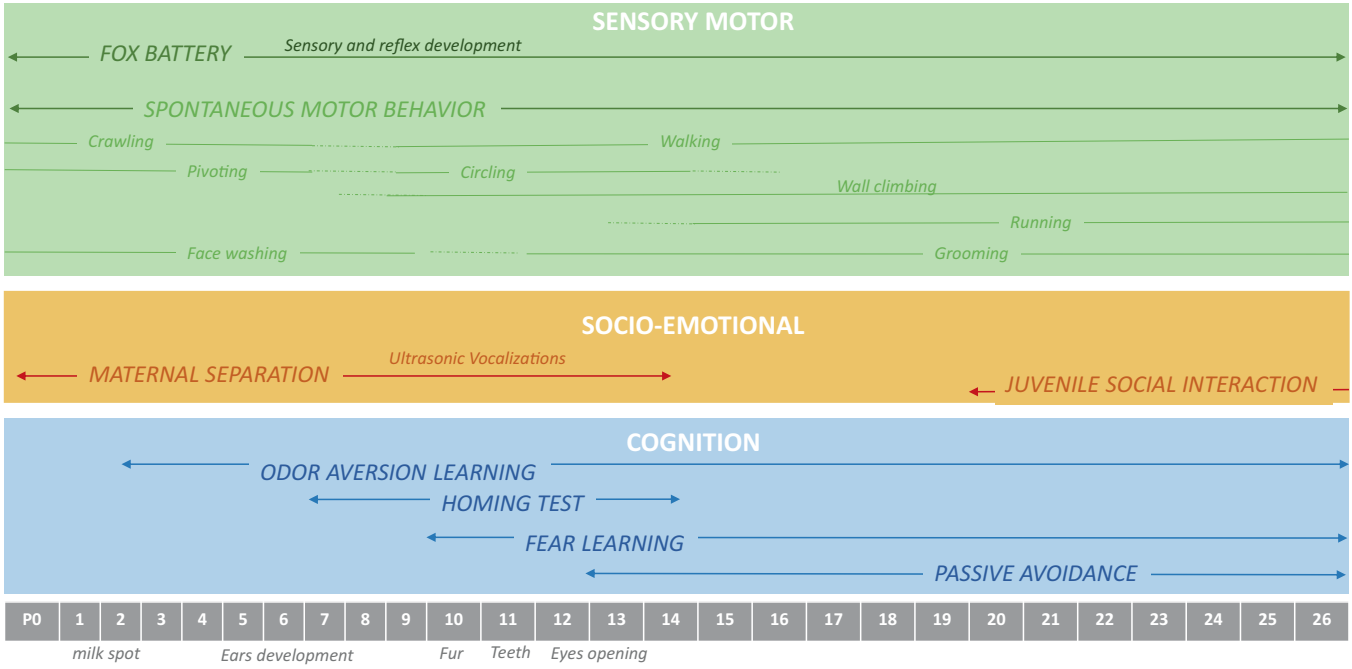

Fig. 2. Behavioral tasks and relative time windows to evaluate neurodevelopment in mouse pups. The development of sensory motor abilities (green) can be evaluated from P1-2 to weaning throughout Fox battery or spontaneous motor behaviors observations. The most analyzed parameters and their relative age of appearance are reported in italics (green). Socio-emotional state (orange) can be assessed using ultrasonic recordings in the first two-weeks of age or with a peer interaction test starting from P20. Cognitive abilities (light blue) can be evaluated with odor aversion or homing test in the first two weeks of age or with tasks based on fear learning starting from P10. Timeline from birth (P0) to weaning (P26) is reported in grey together with the relative stage of physical appearance.

terms of reduction of the number of animals used. This combination also permits to study the relationship between social and motor systems (Armstrong et al., 2020; Michetti et al., 2017b; Romano et al., 2013). In addition, due to the short duration of the session (usually 3 min.) and the limited manipulation of pups, animals employed for USV and spontaneous movement recordings can be tested at adulthood for their social ability. This strategy permits to track the social development of each single animal and in parallel reduce the number of animals used. USVs induced by maternal separation are often used in mouse models of ASD to identify early communication deficits. However, deviation in social development is a general feature of NDD, suggesting that their evaluation could be extended to most of the NDD mouse models.

11. Cognition

Attachment represents a typical behavior of infant rodents that is learned predominantly postnatally, when odor cues are necessary for successful nipple attachment and orientation to the mother and littermates (Wilson and Sullivan, 1994). Thus, almost all the behavioral tasks to assess cognition in pups exploit olfactory abilities. In the past years, authors developed paradigms to allow the study of learning and memory as early as the first two weeks of postnatal life. The homing test has been developed to study the tendency of pups placed in a novel arena to choose a familiar social odor (i.e., a location containing nesting material from the home cage) versus a neutral odor (i.e. fresh bedding) or new odor (material coming from unrelated lactating female) (Bignami, 1996; Chadman et al., 2008; Moles et al., 2004; Scattoni et al., 2008). In addition to the classical homing test, other tasks based on odor associative learning have been developed (Alleva and Calamandrei, 1986; Armstrong et al., 2006). The odor–shock pairings represents an adapted version of the fear conditioning paradigm in neonatal rats (Sullivan et al., 2000). Pups are trained in a classical-conditioning paradigm in which they are exposed to odor paired with shock, or odor only. Four hours after training, pups are tested in a choice task for odor preference. It has been shown that the odor-shock aversion functionally emerges at P10 (Sullivan et al., 2000). The presence of shock aversion at this stage also permits to conduct an adapted passive avoidance task without odor cue starting from P14 (Calamandrei et al., 1996). Thus, based on odor preferences or avoidance paradigms, the study of cognition is possible during the first days of postnatal life. Except for one study in which no deficits have been observed, none of the models analyzed here has been investigated for early cognitive disabilities (Chadman et al., 2008). The implementation of these tasks could provide new evidence in preclinical research focused on NDDs.

12. Epilepsy and EEG recordings

Behavioral seizures are easily evaluated in mouse pups when they appear as a severe phenotype characterized by tonic-clonic attacks. On the other side, slight epileptic behaviors or EEG recordings before PND 20 are very difficult to collect even if they could be very informative for the brain hyperexcitability, especially to track the epileptogenesis process. To this aim few EEG studies in a variety of models for epilepsy or brain ischemia have been conducted, showing the presence of epileptiform activity in very young pups, (Gataullina et al., 2016; Hessel et al., 2009; Kang et al., 2015; Price et al., 2009; Rodriguez-Alvarez et al., 2017; Rodriguez-Alvarez et al., 2015). However, a number of limitations exist for EEG recordings at this stage: (i) rapid maturational changes and brain enlargement in the first weeks of life; (ii) mother's need for all basic functions that prevent cage isolation for recordings (iii) invasiveness of surgical procedures. These evidences clearly show the difficulty to conduct EEG recordings in infants, especially chronic acquisition, but we are confident on the fact that technology will help us in the development of sustainable devices for mouse pups.

13. Conclusions

NDDs are a complex spectrum of behavioral alterations and its diagnosis, intended as classification in one specific NDD, is often difficult. This is mainly due to the complex interpretation of the clinical

manifestations, together with the early onset. No specific therapeutic treatment is currently available for this class of disorders. The use of mouse models may greatly help the understanding of the behavioral domains mainly affected by genetic alterations and therefore facilitate classification, diagnosis and testing of therapeutic treatments. A deep behavioral investigation in mouse pups, covering all behavioral domains (see Fig. 2), could help in the identification of the first circuit/pathway affected by mutations, independently from the main symptom observed. The main manifestations are often associated with a spectrum of conditions and it is important to discriminate if they are due to alterations in a specific brain circuit or to a domino effect coming from other primary symptoms.

In addition, it is also important to consider that concurrently to genetic factors, environmental factors play a role in the etiology of NDDs. A limited number of studies evaluated gene-environment interactions in the development of neurobehavioral phenotype and they are particularly focused on prenatal stress, maternal immune activation and environmental contaminants exposure (Laviola et al., 2006; Malkova et al., 2012; Mullen et al., 2012; Corradini et al., 2018; De Felice et al., 2015; Bachiller et al., 2020; Vigli et al., 2020). However, the impact of environmental factors on synaptic gene functionality is not largely characterized while the study of their intersection could help in elucidating the etiology of NDDs. Thus, the strategies of behavioral testing proposed in the present review could be also applied for the evaluation on environmental models of NDDs.

In conclusion, to characterize models for NDDs and utilize them for elucidation of the disease mechanisms and the preclinical validation of treatments, they need to be employed early in life and with the correct paradigms to identify the onset of the manifestation and track the evolution of the symptoms. Although this is an obvious statement, few papers in the literature of the widely studied murine models for the synaptic genes mutated in NDDs, employed early behavior assessment. We believe that this piece of data is fundamental for our comprehension of synaptopathies and for translating basic and preclinical science into novel therapeutic strategies. To achieve this goal, we invite the community of researchers in the field to implement new behavioral tasks and expand the characterization to the whole neurodevelopmental time window.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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