HHS Public Access

Author manuscript

Autism Res. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Autism Res. 2018 February ; 11(2): 212–222. doi:10.1002/aur.1903.

Loss of Skills and Onset Patterns in Neurodevelopmental Disorders: Understanding the Neurobiological Mechanisms

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Abstract

Patterns of onset in Autism Spectrum Disorder, including a pattern that includes loss of previously acquired skills, have been identified since the first reports of the disorder. However, attempts to study such “regression” have been limited to clinical studies, that until recently mostly involved retrospective reports. The current report reflects discussion that occurred at an NIMH convened meeting in 2016 with the purpose of bridging clinical autism research with basic and translational work in this area. This summary describes the state of the field with respect to clinical studies, describing gaps in knowledge based on limited methods and prospective data collected. Biological mechanisms that have been shown to account for regression early in development in specific conditions are discussed, as well as potential mechanisms that have not yet been explored. Suggestions include use of model systems during the developmental period and cutting-edge methods, including non-invasive imaging, that may afford opportunities for a better understanding of the neurobiological pathways that result in loss of previously-attained skills.

Introduction

On February 19, 2016, the National Institutes of Health (NIH) hosted a workshop on “Loss of Skills and Onset Patterns in Neurodevelopmental Disorders: Understanding the Neurobiological Mechanisms”. Participants discussed the state of the science concerning understanding the variability in onset patterns, particularly the phenomenon of developmental regression, in Autism Spectrum Disorder (ASD) and related disorders. Consideration was given to model systems and cutting-edge methods that may afford

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opportunities for a better understanding of the neurobiological pathways that deviate from typical developmental trajectories. Here, we summarize what is known about onset patterns in ASD, based on the discussion during the meeting, and consider the concept of critical periods for specific skills as a potential clue to underlying biology explaining different onset patterns. Research on Rett Syndrome, a rare genetic disorder that includes regression, is presented as a model for translational research. We then discuss tool development and methods that may ultimately be used for a better understanding of the mechanisms underlying onset patterns in neurodevelopmental disorders, leading to identification of biologically distinct subtypes and treatment targets.

Loss of Skills and Patterns of Onset in ASD

ASD is a neurodevelopmental condition with highly diverse clinical expression, reflecting etiological heterogeneity (Geschwind & Levitt, 2007). Onset in ASD has been a major focus of clinical characterization since the original description by Kanner (1943). Indeed, after initially emphasizing “extreme aloneness from the very beginning of life”, Kanner and Eisenberg (1953) reported “a number of children who reportedly developed normally through the first 18 to 20 months of life… undergo at this point a severe withdrawal of affect manifested by loss of language function, failure to progress socially and the gradual giving up of interest in normal activities”. Similarly, in the first population-based study of autism, Lotter (1966) described 10 of 32 children (31.3%) as having had a “setback” in development, characterized as ‘loss of some ability (mainly in speech) or failure to progress after satisfactory beginning’. Thus, ‘developmental regression’, broadly defined as the loss of previously established skills, was identified as a phenomenon of interest in ASD since the earliest characterizations of the disorder.

Several published reviews have examined rates and correlates of regression in children with ASD, mainly based on parent report (Barger, Campbell, & McDonough, 2013; Rogers, 2004; Stefanatos, 2008; Williams, Brignell, Prior, Bartak, & Roberts, 2015). Three patterns of onset in autism are described: 1) “early onset” (before 12 months); 2) developmental arrest or plateau (e.g., in early language skills), and 3) ‘regressive’ or overt skills loss in one or more domains, occurring in 15–47% (Stefanatos, 2008). A meta-analysis of 85 studies published 1980–2010 by Barger et al (2013) estimated the prevalence of regression at 32.1% (95% CI = 29.5–34.8%). Based on varying case definitions, four regression types were proposed: language alone (24 of 85 studies; 28.2%), language/social, mixed (i.e., including other domains such as adaptive function), and ‘unspecified’. Thus, case definitions often extended beyond loss of verbal language to other aspects of social communication (see also Bernabei, Cerquiglini, Cortesi, & D’Ardia, 2007; Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Goldberg et al., 2003; Luyster et al., 2005). Prevalence varied by type (lowest for language alone) as well as by ascertainment (higher for parent survey or clinic-based estimates and lower for population samples). Mean age of regression was 1.78 years (95% CI = 1.67–1.89 years), regardless of regression type. Regression has also been documented in home video analyses (Goldberg, Thorsen, Osann, & Spence, 2008; Werner & Dawson, 2005) although Ozonoff et al. (2011) reported very low agreement between onset classification based on parent-report vs. independent analysis of videos (kappa = .11; p=.29). In fact, in this study less than half of the participants that evidenced regression on home

videotapes were reported by their parents as having experienced a significant loss of skills, replicating findings from a similar prospective study (Ozonoff et al. 2010) indicating that regression may actually be underreported in retrospective data.

Some studies have found that a history of regressive onset in children with ASD is associated with greater impairments in general, particularly in communication and general adaptive function (Bernabei et al., 2007; Brown & Prelock, 1995; Hansen et al., 2008; Zachor & Ben-Itzchak, 2016). However, findings are inconsistent, with other studies finding no differences (Kobayashi & Murata, 1998; Richler et al., 2006; Siperstein & Volkmar, 2004; Werner, Dawson, Munson, & Osterling, 2005). A history of regressive onset is generally not associated with differences in core ASD symptom severity (Baird, Charman, et al., 2008; L. A. Jones & Campbell, 2010; Lord, Shulman, & DiLavore, 2004; Werner et al., 2005), with the possible exception of social symptoms (Richler et al., 2006; Werner et al., 2005). Again, findings are inconsistent, with Zachor & Ben-Itzchak (2016) and Parr et al. (2011) reporting a general increase in ASD symptom severity in children with a regressive onset, as did Meilleur & Fombonne (2009), although only for regression in domains other than language development, such as motor and self-help skills. Regression is not associated with differences in the initial signs of ASD, as reported by parents (Werner et al., 2005), with the possible exception of early language milestones, although a certain level of expressive language prior to skill loss was needed for coding ‘regression’ (Jones & Campbell, 2010). Such discrepancies in outcomes reported subsequent to reported regression may in fact be accounted for by the low reliability of retrospective report, in contrast to observed loss confirmed by review of home videos taken over time or prospective observational data (Ozonoff et al. 2011), and warrant caution in conclusions drawn from studies that classified regression solely based on retrospective reporting.

With respect to medical comorbidities, children with ASD who had a documented rare metabolic or mitochondrial disorder have been reported to have higher rates of regression than those without such diagnoses (Shoffner et al., 2010). Regression has not been associated with medical factors such as vaccinations (Baird, Pickles, et al., 2008), gastrointestinal problems (Baird, Charman, et al., 2008; Hansen et al., 2008) or epilepsy (Baird, Charman, et al., 2008; Hansen et al., 2008). While Tuchman & Rapin (1997) reported that a history of regression was associated with higher rates of epileptiform activity on EEG, other studies find no differences (Baird, Charman, et al., 2008; Baird, Robinson, Boyd, & Charman, 2006; Hansen et al., 2008). Again, difference may be explained by variable methodology, with one study (Hansen et al. 2008) including more than just language regression as criteria and other studies also differing on methods and definitions.

Onset of autism revisited: findings from prospective research

Longitudinal studies of high-risk infants, often siblings of children with ASD, delineate early developmental trajectories by standardizing data collection methods and drawing on experimental methods from developmental science that tap basic processes (e.g., assessment of visual attention using eye tracking). These studies clarify timing and heterogeneity in symptom onset, and the relationship of regression with later functioning. Reports of atypical trajectories of visual orienting (Sacrey, Armstrong, Bryson, & Zwaigenbaum, 2014) indicate

that disengagement latency in high risk infants later diagnosed with ASD appears typical at age 6–7 months, but actually increases by age 12–14 months (Elsabbagh et al., 2013; Zwaigenbaum et al., 2005). There is also evidence of atypical trajectories of visual attention in the context of face processing in the first 6 months of life, with a decline in fixation to others' eyes characteristic of high risk infants later diagnosed with ASD (W. Jones & Klin, 2013).

While prospective studies provide evidence of subtle social differences by 6 months of age, such as reduced attention to faces (Bhat, Galloway, & Landa, 2010; Chawarska, Macari, & Shic, 2013), overt reductions in social communicative behaviors emerge later in the first year. For example, Ozonoff et al. (2010) found that infants subsequently diagnosed with ASD were indistinguishable from typically developing (TD) infants at 6 months but showed declining trajectories through 36 months in frequency of gazes to faces, directed social smiles and vocalizations, and quality of social engagement. In contrast, TD infants showed stable or increasing trajectories over the same period. Others have reported reduced social engagement and non-verbal communication between 6 and 12 months (Bryson et al., 2007) and atypical language trajectories with declining expressive and/or receptive skills in the second year of life (Landa, Gross, Stuart, & Faherty, 2013). Such trajectories that include loss of these and other skills are sometimes reported in some children with genetic disorders (see Table 1 for details and see Goin-Kochel, Trinh, Barber, & Bernier, 2017), specific language impairment, and even occasionally in typical development (Brignell et al., 2016; Thurm, Manwaring, Luckenbaugh, Lord, & Swedo, 2014). However, results of other studies lead to the conclusion that regression is largely specific to ASD (Baird, Charman, et al., 2008; Pickles et al., 2009).

Prospective ASD studies have measured brain structure and function, providing a window into neural substrates underlying variation in early development and the potential to elucidate mechanisms of regression. Longitudinal neuroimaging studies of high-risk infants subsequently diagnosed with ASD report increased cortical surface area growth from 6 to 12 months, and total brain volume growth rate from 12 to 24 months (Hazlett et al., 2017). There is also evidence that children with ASD from these high-risk cohorts exhibit atypical development of functional cortical connectivity between 6 and 18 months (Eggebrecht et al., 2017; Lewis et al., 2017), which may specifically affect functional networks underlying joint attention skills. While altered experience-dependent neural development may account for reciprocal, cascading effects between emerging behavioral features and altered neuronal circuitry (Estes et al., 2015), few studies have assessed differences in brain developmental patterns by accounting for onset patterns including regression. Nordahl et al., (2011) had previously reported that accelerated head growth between ages 6 and 18 months was associated with parent-reported regression in 180 preschool children with ASD. Ultimately, brain imaging studies, particularly when conducted prospectively with concurrent observations of behavioral development (including any declining skills), provide a macro-level understanding of potential structural brain differences, activity and functional connectivity related to regression. Such knowledge at the cellular and molecular level may provide a path for treatment or prevention.

Neurobiological mechanisms of regression

A close look at mammalian brain development provides insight into potential mechanisms of onset of symptoms and regression of skills. The human brain forms during gestation and continues to mature into adulthood, with vibrant growth in the early postnatal periods. The diverse cell populations are specified and generated in overlapping cohorts. The bulk of the neurons are born in the first and second trimesters, followed by the astrocytes and then oligodendrocytes during the third trimester and the first year of life (Semple, Blomgren, Gimlin, Ferriero, & Noble-Haeusslein, 2013). The positions and types of neurons provide the basic framework for the brain regions and circuits. Pathology of postmortem samples have found altered neuronal numbers in Down's syndrome (Guidi et al., 2008), tuberous sclerosis (Marcotte, Aronica, Baybis, & Crino, 2012), and ASD (Blatt & Fatemi, 2011; Courchesne et al., 2011; Hutsler & Casanova, 2016; Packer, 2016). In ASD, the majority of the studies indicate little or no change in cell number, but disrupted architecture has been noted. It should be noted that many samples are from adults, and the timeframe for the apparent changes in cell numbers is unknown. Misplaced neurons have been observed in postmortem tissue and animal models of ASD (Morgan, Barger, Amaral, & Schumann, 2014; Packer, 2016; Stoner et al., 2014), and changes in cellular organization or location have the potential to dramatically disrupt circuit formation and function (Bailey et al., 1998; Hutsler & Casanova, 2016). Thus, the initial steps in neuronogenesis and migration establish the initial framework and direct subsequent brain growth and function.

The expansion of the glia cells, astrocytes and oligodendrocytes is dependent upon the pool of remaining neuronal progenitors and neuronal activity (Benediktsson et al., 2012; Gallo et al., 1996; Ge, Miyawaki, Gage, Jan, & Jan, 2012; Spitzer, Volbracht, Lundgaard, & Karadottir, 2016). The early expanding brain volume observed in a subgroup of children with ASD may result from aberrant glial ontogeny (van Dyck & Morrow, 2017). Increased levels of astrocyte markers were found in postmortem studies of ASD (Crawford et al., 2015; Fatemi, Folsom, Reutiman, & Lee, 2008); however, the onset of the increased expression is unknown. In animal models of ASD, cerebral cortical astrocytes directly contribute to aberrant synaptogenesis and plasticity in the first postnatal month, a timeframe that corresponds to when regression observed in children (Carson, Van Nielen, Winzenburger, & Ess, 2012; Maezawa, Swanberg, Harvey, LaSalle, & Jin, 2009; Magri et al., 2013). White matter abnormalities are frequently reported from imaging studies of ASD (Hazlett et al., 2005; Wolff et al., 2015); yet the underlying cause(s) whether due to less compact myelin, excessive axon growth, or persistent connections (lack of pruning) are not known (Lainhart, 2015). The underlying neurobiology of tract formation and synaptic pruning has not been examined in animal models of ASD during early postnatal ages corresponding with regression. The cellular bases for the increased brain volume observed in children with ASD are hypothesized to include glial origin but definitive studies are needed.

There is now evidence of postnatal altered trajectories of brain volume in children with ASD, occurring during the period of heightened neuronal circuit formation involving synaptogenesis, which peaks at 2 years (Lenroot & Giedd, 2006; Semple et al., 2013). The first neuronal circuits are established in the embryo shortly after neurons are born (Chun & Shatz, 1988; Kostovic & Rakic, 1990). The cerebral cortical areas are established during the

fetal period and remodeled during the first two years of life (Kostovic et al., 2014). Recent studies coupling imaging techniques with histological data suggest that cerebral cortical regionality may be correlated with developmental and behavioral milestones (Kostovic et al., 2014; Vasung et al., 2016).

Throughout childhood, circuits are initiated, remodeled and stabilized as skills are learned and mastered (Levitt, 2003). As the brain reaches the age and configuration of the adult, rates of synaptogenesis and synaptic pruning slow dramatically. Many initial synapses are temporary, since these initial connections guide later neuronal migration or provide inputs to transient embryonic structures. In some cases, early circuits with multiple connections are refined to a single or few pathways dependent upon sensory inputs (Martini, Moreno-Juan, Filipchuk, Valdeolmillos, & Lopez-Bendito, 2017; Wiesel & Hubel, 1963). If the target neurons (or a subpopulation thereof) are absent or misplaced, then the initial circuit may be altered or show limited remodeling, thus impeding skill acquisition or maintenance (Borrell et al., 1999; Hong et al., 2000; Weeber et al., 2002). In severe cases, neuronal migration disorders are the cause of epilepsy and intellectual disability (Crino, 2011; Hong et al., 2000; Lukose, Beebe, & Kulesza, 2015). Little is known about milder phenotypes with a small fraction of misplaced neurons or missing neurons. However, postmortem samples obtained from adults with ASD reported reduced numbers of inhibitory neurons expressing the neurotransmitter GABA (gamma-amino butyric acid) (Blatt & Fatemi, 2011; Lawrence, Kemper, Bauman, & Blatt, 2010). It is unknown whether the deficiency was present in early life or whether the potential loss of inhibition affected skill acquisition or loss.

During typical neurodevelopment, the neural circuitry of the sensory systems matures first, followed by motor, association, and integrative regions. Classical experiments in the visual and auditory systems have demonstrated that critical periods define establishment of adult (mature) circuitry and function (Hensch & Bilimoria, 2012). In children, critical periods have been recognized for vision, audition, language learning, and possibly musical ability and memory (Meredith, 2015). In animal studies, early closure of a critical period(s) delays or halts progress to the final circuit configuration or skill acquisition (Erzurumlu & Gaspar, 2012; Gavornik & Bear, 2014). Similarly, failure to open or close the critical period prevents expected maturation. Loss of skills may represent the integration of incorrectly timed or incomplete critical periods and aberrant circuit formation (LeBlanc & Fagiolini, 2011). Experimental work that tests phenotypic outcomes based on timing, location, and mechanisms of such circuit formation is required to test abnormal processes during critical periods. The over-pruning hypothesis of autism describes how the timing of aggressive synaptic pruning provides a computational basis for the diverse developmental trajectories observed in ASD, including regression (Thomas, Davis, Karmiloff-Smith, Knowland, & Charman, 2016). While the concept of critical periods has been applied to relevant developmental areas such as sensory systems and language, less work has addressed social-communication development specifically.

Rett Syndrome as an example of translation

Another method for gaining insight into potential mechanisms of regression in ASD is translational research that characterizes specific neurodevelopmental disorders with clear

regressive features. Rett syndrome (RTT), a neurodevelopmental disorder that primarily affects girls and is usually caused by mutations in Methyl-CpG-binding Protein 2 (MECP2; Neul et al., 2008), is characterized by distinct regression with loss of acquired spoken language and volitional hand use (Neul et al., 2010). Although the distinct motoric abnormalities in RTT such as loss of hand skills, dyspraxic gait, and a variety of movement abnormalities are very distinct from clinical problems commonly observed in autism, aspects of regression in RTT may point to common mechanisms. For example, the loss of spoken language observed in RTT may be similar to language loss and dysfunction observed in autism. Additionally, the typical time for regression in RTT is 18–30 months of life (Neul et al., 2014), similar to timing of language loss in ASD (Barger et al., 2013), although prospective study in ASD reveals an earlier loss in more subtle social communication (Ozonoff et al., 2010).

There are features of Rett syndrome that make it attractive to understanding pathogenic mechanisms of regression. First, clinical diagnoses of Rett syndrome typically include mutations in MECP2, ensuring that clinical studies in this disorder are evaluating a consistent etiology. Second, there are excellent models of the disorder, including multiple genetically engineered rodents (Katz et al., 2012; Veeraragavan et al., 2016) showing high levels of face validity by reproducing many clinically relevant phenotypes, and cellular models based on human iPSC (Induced pluripotent stem cells) (Marchetto et al., 2010). Progressive loss of proper breathing regulation is shown in a RTT mouse model (Huang et al., 2016) and regression of forepaw skills is shown in rats (Veeraragavan et al., 2016). Recent work demonstrates similarities in altered visual evoked potentials (VEP) in both the RTT mouse model and affected people (LeBlanc et al., 2015). In RTT mice there is a decline in VEP with age and phenotypic severity, and in humans there are VEP abnormalities after regression. This raises questions about the role of the maturation of the excitatory/inhibitory (E/I) neural circuitry.

Interestingly, research using RTT animal models has identified commonalities with other animal models of neurodevelopmental disorders. Gogolla et al. (2014) identified abnormalities in multisensory integration of auditory and tactile stimulus in the insular cortex of RTT mice like adult Shank3 null mice, Gad65 null mice, and BTBR mice (a model of autism). These abnormalities all point to disrupted postnatal GABA circuit maturation, and MeCP2 function has been shown to be critical within GABAergic neurons (Chao et al., 2010), reiterating the importance of E/I balance development and maturation in neurodevelopmental disorders. Additionally, animal models have revealed commonalities in the role of primary tactile sensory circuitry in the development of various behavioral features. Multiple neurodevelopmental models show abnormalities of primary tactile sensation, and MeCP2 dysfunction within primary sensory neurons leads to anxiety, social interaction abnormalities, and locomotor problems (Orefice et al., 2016).

This developing framework for understanding the pathogenic mechanisms that underlie regression in RTT may be exemplar for understanding regression more generally. However, there are challenges to overcome before effectively translating information from RTT animal models into human studies in RTT and ASD. First, both RTT and other neurodevelopmental disorder/ASD models need to be characterized in greater depth, including at important

neonatal and juvenile stages, and at both behavioral and neural circuit levels, to identify features of regression. Second, because RTT is defined by regression of specific skills, most individuals are not identified until after regression, making human studies before and during regression challenging. Third, the bulk of animal work in RTT has focused on hemizygous mutant male animals, which represent a distinct clinical condition from the heterozygous mutations observed in girls and women with RTT, although recent research has identified clear phenotypic abnormalities in heterozygous mutant female mice (Samaco et al., 2013). Finally, there is a great need for methodologies to connect information between animal models and affected humans (Hammock, Law, & Levitt, 2013; Ku, Weir, Silverman, Berman, & Bauman, 2016; Sukoff Rizzo & Silverman, 2016). Non-invasive methods such as evoked potentials provide a suitable approach, and it will be worthwhile to expand the use of imaging modalities across species to assist in our understanding of common mechanisms.

Recommendations and Next Steps

Prospective longitudinal studies of infants at risk for ASD, and innovative methods and tools for characterizing behavior early in life have revealed variability of onset patterns in ASD. Patterns include loss of specific skills, and are usually characterized by variability among domains of functioning and across development, with emphasis on changes in the first few years. However, such variability is not unique to ASD. A cross-syndrome approach may help identify aspects of onset patterns (type, timing, sex differences) that are specific to ASD or subtypes of ASD. It is clear that regression is not a discrete event but a process, and it is dimensional rather than categorical. More precise, prospective, frequently administered and comprehensive measures of features undergoing decline, and the corresponding brain changes, are needed. It may be informative to compare children who appear to lose skills early on but do not develop ASD with those who do.

Some potentially powerful imaging techniques (e.g., radioactive PET tracers) are limited for use in neurodevelopmental disorders. Alternative noninvasive and non-sedating methods are needed to define typical development of the neural pathways and their activation in children, and assess how these develop in children who experience loss of skills.

There is a need to further investigate early sensory and motor development in ASD, as these may be detectable prior to social orienting and social attention differences, and may be conducive to systems modeling and even reversal. Although neural connectivity has not been well studied in this developmental period in rodents or primates, and might be difficult to accomplish, the effort is one worth considering. There is a need to understand the various neurobiological processes of synaptogenesis and pruning in ASD and other neurodevelopmental disorders, using disease models, limited post-mortem samples, and novel non-invasive methods to assess synapse formation and pruning in people.

Finally, there is a need to better understand typical development, as well as atypical development, in animals and model systems. There are known sex differences in both the development and expression of ASD, and there is a need for more animal research that considers both sexes. Animal models of syndromic conditions that involve regression, such as RTT, are important tools for understanding the neurobiology underlying onset patterns. It

is challenging to assay behavior in early development in most animals, but paradigms for assessing adult behaviors might be re-tooled to evaluate developmental trajectories and regression.

Acknowledgments

We would like to thank all of the participants of the NIMH workshop "Loss of Skills and Onset Patterns in Neurodevelopmental Disorders: Understanding the Neurobiological Mechanisms" including Frank Avenilla, National Institute of Mental Health (NIMH); Katarzyna Chawarska, Yale University; Susan Daniels, NIMH; Lisa Gilotty, NIMH; Sharon Juliano, Uniformed Services University of the Health Sciences; Annette Karmiloff-Smith, University of London; Alice Kau, Eunice Kennedy Shriver National Institute of Child Health and Human Development; Keerthi Krishnan, Cold Spring Harbor Laboratory; Cindy Lawler, National Institute of Environmental Health Sciences; Jason Lerch, University of Toronto; Laura Mamounas, National Institute of Neurological Diseases and Stroke; Eric Morrow, Brown University; Alysson Muotri, University of California, San Diego; Charles Nelson, Boston Children's Hospital; Karen Parker, Stanford University; Elliott Sherr, University of California, San Francisco; Jill Silverman, MIND Institute/University of California, Davis; Jason Wolff, University of Minnesota. This work was supported by the Intramural Research Program (Thurm, 1ZIAMH002868) and the Office of Autism Research Coordination of the NIMH. Other support includes is funding from NIH (Neul, Powell, Zwaigenbaum), Rettsyndrome.org (Neul), Rett Syndrome Research Trust (Neul), Eloxx Pharmaceuticals (Neul), Canadian Institutes of Health Research (Zwaigenbaum), Kids Brain Health Network (Zwaigenbaum), Brain Canada – Azrieli Foundation (Zwaigenbaum),Autism Speaks/Autism Speaks Canada (Zwaigenbaum), Glenrose Rehabilitation Hospital Foundation (Zwaigenbaum), Stollery Children's Hospital Foundation (Zwaigenbaum), Womens and Children's Health Research Institute (Zwaigenbaum).

Disclosures: This work is based on a workshop sponsored by the National Institute of Mental Health, National Institutes of Health, and held on February 19, 2016. The opinions and assertions contained in this article are the private views of the authors and are not to be considered as official or as reflecting the views of the Department of Health and Human Services, the National Institutes of Health, or the NIMH or NIAAA.

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LAY ABSTRACT

Loss of previously acquired skills, or regression, has been reported in Autism Spectrum Disorder since Kanner's reports in the 1950's. The current report reflects discussion from an NIMH convened meeting in 2016 with the purpose of bridging clinical autism research with basic and translational work in this area. This summary describes the state of the field regarding clinical studies and suggests use of model systems during the developmental period and cutting-edge methods, for a better understanding of the neurobiological pathways that result in loss of previously-attained skills.

Table 1

Example Reports of Regression in Syndromes Associated with Autism Spectrum Disorder

Condition	Report	Ages/Stages	Specific Skills Lost	Associations?
Kleefsta Syndrome	Kleefstra et al. (2009)	Various ages	toileting, eating, loss of interest, undefined	
Phelan-McDermid Syndrome	Denayer et al. (2012) Serret et al. (2015)	Not reported 12–13 years	language, fine motor, gross motor, daily living skills, social engagement	
	Reierson et al. (2017)	Range from 18 months to 18 years		
Christianson Syndrome	Pescosolido et al. (2014)	Range from 15 months to 16 years	Language (words or sounds) (57%); walking (57%), eating (14%) fine motor (14%) eye contact/facial expression (14%)	
15q Duplication	Conant et al. (2014)	Not reported		20/33 cases associated with epilepsy
Rett Syndrome/CDKL5	see Neul et al (2010; 2014) for reviews	Most often between 6 & 30 months	fine motor; language; gross motor	
Down Syndrome	Castillo et al. (2008)	Language Loss $\overline{x}=62$ months Other skill loss $\overline{x}=46$ months	language loss; other skills (not specified)	