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Retrospective Reports of Skill Attainment and Loss in Phelan-McDermid Syndrome

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Abstract

Phelan-McDermid syndrome (PMS) is a genetic condition associated with profound neurodevelopmental disabilities. This study described patterns of onset and loss of developmental milestones and associated skills using questionnaire data from the PMS International Registry (N=374) and clinician-led assessment data from the Developmental Synaptopathies Consortium natural history study (N=207). Across studies, an overwhelming proportion of individuals with PMS were reported to be delayed in acquiring basic skills, and skill loss/regression was commonly reported across several types of developmental skills, including some after age 10 years. The current descriptive study synthesizes two complementary data sources showing loss occurring in the context of significant delays and frequent lack of milestone attainment in individuals with PMS. Further work to elucidate mechanisms is needed.

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INTRODUCTION

Phelan-McDermid syndrome (PMS) is a genetic condition defined by either a loss of function variant in the SHANK3 gene, or a deletion at the terminal end of chromosome 22 (Phelan et al., 2022; Phelan et al., 1993). PMS is associated with intellectual disability and often severe motor impairments, absence of speech, behavioral disorders, and neurologic diagnoses such as epilepsy(Soorya et al., 2017). Major milestones are very commonly delayed or not met; of the 146 participants in one of the largest PMS studies, 88% did not walk before age 3 years, 50% had no words at the time of assessment, and 77% used fewer than 40 words (Sarasua et al., 2014). The severity of delays, like that of eventual disability, appears to be related to deletion size (Yin et al., 2024).

Even in the context of delayed or missing major milestones, individuals with PMS may exhibit a decline or loss of skills from levels previously achieved (Denayer et al., 2012; Sarasua et al., 2014; Vucurovic et al., 2012). In some cases, losses occur subsequent to seizures or other medical problems (Denayer et al., 2012; Kolevzon et al., 2014), but not always (Reierson et al., 2017). Neurodegenerative (Vucurovic et al., 2012) or psychiatric illness onset processes (Kolevzon et al., 2019) have also been proposed as an explanatory factor in these losses; a recent case series described this pattern in 66% of 38 individuals, with loss occurring as late as the fourth decade of life (Kohlenberg et al., 2020). Other work suggests that these later losses may be more reliably associated with acute events such as sickness or stress (Dille et al., 2023).

Loss of skills, often referred to as regression, has been studied within the context of the diagnosis of idiopathic autism spectrum disorder (ASD; Barger et al., 2013), but it has also been conceptualized in the broader framework of neurobiological developmental processes and mechanisms (Thurm et al., 2018). Increasingly, developmental regression is understood to be an important shared feature of many genetic conditions associated with neurodevelopmental disorders (Marschik & Bölte, 2019). It has been explored as a pathognomonic feature of specific genetic conditions associated with neurodevelopmental problems, such as Rett Syndrome (Neul et al., 2010; Smeets et al., 2019), and recently has been described in a variety of other genetic conditions associated with neurodevelopmental disability (Goin-Kochel et al., 2017; Hahn et al., 2015; Pescosolido et al., 2014). Importantly, while a significant focus of research has been on regression in early life, as mentioned above, there is evidence for significant

neuropsychiatric changes and associated regression in late adolescent and/or early adulthood in some conditions (Kleefstra & de Leeuw, 2010; Kohlenberg et al., 2020).

In this study, we synthesize complementary retrospective data from a registry study and a natural history study to describe the attainment and loss of developmental skills among individuals with PMS. We contribute to the literature by providing a detailed description of commonly reported developmental skills, including those recognized (Sheldrick & Perrin, 2013; WHO Multicentre Growth Reference Study Group, 2006) as communication (words and phrases) and gross motor (walking) milestones, which may be tracked by pediatric providers in order to prospectively identify delays and losses.

Methods

Phelan-McDermid Syndrome International Registry (PMSIR)

Data used in the preparation of this article were obtained from the Phelan-McDermid Syndrome Foundation from the Phelan-McDermid Syndrome International Registry (PMSIR; Kothari et al., 2018) (access date December 31, 2020). The study was approved by the Advarra Institutional Review Board, and informed consent was obtained from all caregivers. Caregivers of individuals with PMS enrolled in the PMSIR, a database of approximately 1,100 individuals. A subset (n=562) of these individuals uploaded genetic reports, which were curated and reviewed by genetic counselors and a clinician subject-matter expert to confirm PMS diagnosis. The PMSIR was closed to new enrollment at the time of data export for this project, and has since been adapted into the ongoing PMS DataHub. No new data from the PMS DataHub is included in this report.

Participants were included in this analysis if they had a confirmed PMS diagnosis and completed the Developmental Questionnaire, one of several forms included in the PMSIR (n=374). The Developmental Questionnaire is a caregiver survey that captures information about the proband's early history, including the acquisition (at the individual skill level) and/or loss (at the domain level) of skills across communication (seven skills, acquisition only), motor (10 fine motor skills and nine gross motor skills), self-help (six skills), and social (domain-level only, loss only) domains. Parents selected the appropriate age category from among mutually exclusive response options (e.g., "0 – 3 Months", "4 – 7 Months"), which included "Not applicable" and "Unsure." The response categories proceed from "31 – 36

months" to "4 – 5 years" and it is not known how parents indicated an age that was between these (e.g., 3 years, 4 months). For all items, a choice of "Unsure" was recoded as missing. Some participants had multiple administrations; for the purpose of analysis we selected the latest available version to give the child maximal amount of time to have acquired the skill.

Developmental Synaptopathies Consortium Natural History Study (DSC)

Participants. As of November 2023, when the data for this paper were extracted, 208 participants with PMS had enrolled in a six-site prospective, observational cohort study evaluating the genotype, phenotype, and natural history of PMS, conducted by the DSC (NCT02461420). The first phase of this study enrolled participants from 2015 to 2020; the second phase began in 2021 and is ongoing. Sites are the Icahn School of Medicine at Mount Sinai, Boston Children's Hospital, Rush University Medical Center, Stanford Medical Center, the National Institute of Mental Health, and University of Texas Southwestern Medical Center. Participants were recruited through advertisement to PMS parent groups and through the Rare Disease Clinical Trials Network website (https://www.rarediseasesnetwork.org/). This study was approved by the Boston Children's Hospital Institutional Review Board and acknowledged by IRBs at participating sites. English-speaking males or females, initially for ages 3-21 years, and then expanding to individuals over age 18 months, with confirmed pathogenic deletions or sequence variants affecting the *SHANK3* gene were eligible for inclusion in the natural history study. Participants with at least one of the measures described below were included in the current study, N = 207.

Measures. This study included an in-person neurodevelopmental assessment in addition to extensive semi-structured interviews with experienced clinicians. The tools used to obtain information on milestone acquisition and loss are described below.

Baseline Medical History Form. This form was completed by the clinician at baseline only, and comprised information from both parent interview and chart review. A subset of variables were used in the current analysis: whether or not three major milestones (walking, words, and phrases) had been attained, and if they had, the age of acquisition. Most participants (n = 193, 93%) had this form.

Autism Diagnostic Interview-Revised (Rutter et al., 2003). The ADI-R is a semi-structured, standardized instrument used to obtain information for the diagnosis of ASD. The ADI-R was completed by the clinician, via parent interview, at baseline only. For this report, we used only the items regarding milestone (walking, first words, first phrases) attainment. One hundred forty-one (68%) participants had at least some data on this form.

Regression Supplement. The Regression Supplement is a clinician-led parent interview that was modified from an existing instrument (Thurm et al., 2014). At each visit, the parent was asked about the acquisition and loss of specific skills in three domains: socio-communicative behaviors (six items), gross motor (seven items) and fine motor (three items). For each item, the parent indicated whether the child had ever attained the skill, defined as consistently present for at least one or three months (depending on the skill), and the age of attainment. If the skill had been attained, the parent indicated whether and at what age the skill had been lost, defined as the individual stopping doing this skill for a period of at least 3 months. The last available form for each participant, reflecting cumulative acquisition and loss, was used in the current report. This form was administered only in the first phase of the study and was available for n = 96 (46%) participants.

Early Skill Attainment and Loss (ESAL). This measure queries the age of acquisition, age of loss, and age of regain of 17 skills in four domains (Motor, Language, Social Communication, and Daily Living). Specifically, it asked whether and at what age a skill had ever been attained, if so, then whether and at what age the child ever stopped performing the skill, and if so, whether and at what age they restarted the skill. This form was administered only in the second phase of the study, and was available for n = 77 (37%) of participants; for 13 of these, it was administered as a direct online survey to parents.

Data processing. Two measures, the Baseline Medical History Form and the ADI-R, were obtained in both phases of the study. The Regression Supplement was obtained only in the first phase, and the Early Skill Attainment and Loss form was obtained only in the second phase. Thus, for this report, data were combined across measures in the following manner. Because the ADI-R and Baseline Medical History forms may have been contemporaneously administered, a composite was created wherein the ADI-R data were used if available, and if not, the Baseline Medical History data were used. An interim dataset containing all administrations of the combined ADI-R and Baseline Medical History, the

Regression Supplement, and the ESAL was then compiled. For some skills in the social domain, the age of acquisition response scales differed between the ESAL (before or after 12 months) and the Regression supplement (exact age), and so data for these skills were all converted to categorical (before or after 12 months). Next, for each skill within each participant, the most recent data were selected, in order to provide as much study time as possible for the child to have developed and/or lost the skill. For example, if a participant had acquisition/loss data for first words from the ADI-R at age 8 and the ESAL at age 10, the ESAL data were used. For a given skill within a given person, if the ages of acquisition/loss from two forms (e.g., ADI-R and ESAL) were available at the same timepoint and did not agree exactly, their median was used. As a result, the analysis dataset has a slightly different sample for each skill.

Statistical Analysis

The goals of this study were descriptive, and no hypothesis tests were performed. To describe the rates of acquisition, we use raw numbers and proportions, noting the denominator when it was not the full sample. Confidence intervals (95%) were calculated using the binom package for R (Dorai-Raj, 2022). The normal approximation was used unless n(1-p) or n(p) was less than 5, or p or 1-p was less than .10, in which case the Clopper-Pearson exact method was used. For age of acquisition and loss data, which were ordered categories in PMSIR and continuous in the natural history study, as well as current age when a skill had not yet been acquired, we use the median and interquartile range to describe the distribution. To contextualize the acquisition ages for certain communication and gross motor milestones, we compare study results to normative data from the World Health Organization (WHO) (WHO Multicentre Growth Reference Study Group, 2006) and the Centers for Disease Control (CDC) (Sheldrick & Perrin, 2013; Sheldrick et al., 2019).

Results

PMSIR Survey

Caregivers of 374 individuals with PMS responded to the Developmental Questionnaire (see **Table 1** for demographics). For most domains, the rate of missing data was high (6 – 33% across the Communication, Fine Motor, and Gross Motor domains and 24 – 57% across Self Help domains).

Acquisition (yes/no) and age of acquisition for specific skills are described in **Table 2** and **Figure 1**. Use of words was not attained in 43% (n=133) of those with non-missing data (n=312), and for the 57% (n=179) who attained it, the median age was 19 – 24 months. Thus, for individuals who did attain use of words, it was delayed relative to the CDC cutoff of 18 months. A sizeable minority of the sample (18%, n=63 of 353 with non-missing data) had not yet attained walking, and the median age of walking of the 82% (n=290) who had was 19 – 24 months. This age of walking acquisition exceeds the 99th percentile of the normative distribution provided by the WHO. The missingness rate in the Self-Help domain was very high, and so results must be interpreted with caution. The majority of respondents indicated that the individual with PMS had acquired the ability to drink (93% of non-missing) and to feed themselves (93% of non-missing), while only about half of the individuals with PMS were able to dress themselves (51% of non-missing), toilet independently during the daytime (52% of non-missing), or toilet independently during the nighttime (42% of non-missing).

Skill loss was queried for domains (Fine Motor, Gross Motor, Self-Help, Social) and is summarized in **Table 3**. Rates of skill loss across the fine motor, gross motor, self-help, and social domains ranged from 24 – 39% among those with non-missing data. Across the full sample (N=374), 8% (n=31) reported loss in all four domains, 13% (n=47) in three domains, 13% (n=47) in two domains, 22% (n=84) in one domain, and 44% (n=165) reported no loss in any domain. When skill loss in any domain did occur, it most frequently occurred in the 1 – 2 year age range, but loss after the age of 10 years was not uncommon. Across all of the domains, approximately one-third reported not having regained the reported losses at the time of the survey.

DSC Natural History Study

The total DSC natural history study sample comprised 207 children, adolescents, and adults with at least some data on skill acquisition and loss (see **Table 1** for demographic data). Summary statistics for acquisition are shown in **Table 4** and **Figure 2.** The lack of attainment of many communication skills was very high. More than half of the sample (n=108 of 197, 55%; median age = 6 years) had not attained phrase speech, 33% (n=65 of 196; median age = 6 years) had not acquired single words, and 23% (n=27 of 115) had not acquired babbling. The participants who *had* developed single words and phrase speech

by the time of the assessment reportedly acquired these skills much later than expected in typical development. The majority of participants acquired the most basic social skills (smiling, 88%; eye contact, 79%, responding, 92%), but only about half of participants acquired the more advanced skills of showing (n=69 of 135, 51%), pointing (n=74 of 138, 54%), and waving (n=68 of 136, 50%). While the majority of participants acquired most of the motor skills that were assessed in this study, the rate and extent of delay in walking was significant. At least half of the sample began walking independently no earlier than 17 months—an age that exceeds the WHO 99th percentile. The non-acquisition of toileting skills was notable; only 41% (n=30 of 74) achieved bladder continence and 37% (n=28 of 75) achieved bowel continence.

The loss of skills was common across domains (Table 5). Nearly half of participants who acquired words lost them (n=26 of 54 respondents), and 34% (n=12 of 35 respondents) who acquired phrase speech lost it. The rate of loss for social skills ranged from 14% (n=9 of 66 for showing) to 27% (n=18 of 67 for waving). The rate of loss of walking ability was very low, but not zero (n=5 of 128, 4%). Loss of other motor abilities was similarly rare, but 33% (n=10 of 30) of those who acquired bladder continence lost the ability.

Discussion

The natural history of a syndrome includes both the early developmental course and later symptom manifestations, and both are necessary to identify the earliest and most important treatment targets. In the absence of reliable observational data from prospectively studied birth cohorts, however, our understanding of skill acquisition and loss is necessarily rooted in retrospective report. In this descriptive study, we synthesized information from two types of study designs (a natural history study and an online registry) and two types of ascertainment method (clinician-led interview and parent survey) to contribute the largest and most detailed report on the developmental history of PMS to date. Echoing other research, we found clear evidence of pervasive and widespread delays in milestone acquisition across all areas of development, but especially in basic communication and gross motor skills. Importantly, we also documented high rates of non-acquisition of a variety of skills that are nearly uniformly attained at early ages in the general population. Neither source reported that more than two thirds of the sample had

attained use of single words, for example, and the median age for those who did was well beyond the cutoff for being considered delayed in both samples. High rates of non-acquisition for toileting skills were observed in both samples, and most non-attainers were at least adolescents, marking toileting an area of significant impact on quality of life for the individual and their caretakers. For many of these skills, the age of the children who had not yet attained the skills suggests that they are unlikely to ever meet the milestone (Pickett et al., 2009). Taken together, these studies support the conclusion that individuals with PMS are likely to experience pervasive and widespread delays, and even non-acquisition, of important skills during development.

Skill loss is inherently more difficult to ascertain than skill acquisition (Thurm et al., 2018), and there is evidence that methodology dramatically impacts rate estimates (e.g., retrospective versus prospective, observation versus parent report, definition of loss) (Ozonoff & Iosif, 2019). The two studies reported on here queried loss at different levels: the survey at the domain level and the natural history at the skill level. Thus, synthesizing the two requires some degree of inference. Both studies found that more than one-third of the sample had experienced loss in some skill or domain, and remaining differences might be considered in the context of parents thinking of all possible behaviors (registry survey) versus individual skills which a participant may have lost one or more of (natural history study). Within the registry, 56% of parents reported loss in at least one area. The clinician-led interviews in the natural history study indicated that 33% of the sample had lost at least one of the specific skills queried. Thus, the combined cohorts indicate that even when skill acquisition occurs, individuals with PMS appear to be at significant risk of skill loss. These results confirm earlier reports (Sarasua et al., 2014), and fortify the knowledge base by demonstrating similar findings across the registry-based survey study and the clinician-led natural history study.

Normative data are useful in contextualizing the patterns of skill acquisition and loss observed in these studies. However, given what is known about the phenotype of PMS, such as the high rate of intellectual disability, it is perhaps even more informative to consider the results of these studies in comparison to neurodevelopmental disorder l populations. For example, delayed acquisition of skills seen in the PMS sample in the current paper is similar to the severe delays (i.e., greater than 6 months beyond expected norms) in many other rare genetic conditions associated with neurodevelopmental disorder

(q21.1 deletion, 1q21.1 duplication, 16p11.2 deletion, 16p11.2duplication, ADNP, ASXL3, CSNK2A1, DYRK1A, GRIN2B, MED13L, PACS1, PPP2R5D, SCN2A, SLC6A1, STXBP1, SYNGAP1) (Wickstrom et al., 2021). Indeed, Wickstrom et al. (2021) found that ≥50% of the sample of participants with single-gene disorders had severe delays for acquisition of single words and combined words. However, the rates of non-attainment of milestones in these samples are considerably higher than those found in individuals not ascertained based on genetic conditions with autistic disorder, Pervasive Developmental Disorder-Not Otherwise Specified, or developmental delay (Thurm et al., 2014).

The high rates of delay and loss observed in these samples underscore the critical need for careful monitoring of the early development of children with PMS. While currently many children are not diagnosed with PMS within the first few years of life, the risk of significant delays in important developmental milestones necessitates that early intervention begins as soon as possible, as is recommended for other rare genetic conditions associated with neurodevelopmental disorders (Bishop et al., 2017). Early intervention services are critical in order to facilitate the initial development of skills as well as the maintenance of acquired skills for as long as possible. Given the significant early developmental delays, the diagnosis of PMS alone should indicate referral for evaluation for early intervention services, as Part C of the Individuals with Disabilities Education Act states that each state must provide these services to infants and toddlers with diagnosed physical or mental conditions with a high probability of resulting in developmental delay ("Individuals with Disabilities Education Act," 2004).

While neither of these studies comprehensively collected information regarding significant events preceding the participants' loss of skills, prior research has documented a number of suspected triggers across cases. Several studies have found that regression within this population has been associated with the onset of seizures (Kohlenberg et al., 2020; Soorya et al., 2013); however, this finding is not universal across studies (Reierson et al., 2017). Other documented antecedents of regression in PMS, including in adolescence or later, have included the onset of psychiatric illnesses, menstrual cycling, acute infections, and psychosocial stressors (Kohlenberg et al., 2020). Similar episodes have been documented in other neurogenetic syndromes, including Kleefstra syndrome (Kleefstra & de Leeuw, 2010), Christianson syndrome (Pescosolido et al., 2014), Down syndrome (Dykens et al., 2015), Williams syndrome (Valdes et al., 2018), and 22q11.2 deletion syndrome (Schneider et al., 2014). Future research should include the

level of detail in interviews which would be necessary to establish such relationships, in addition to employing a sample with a wide age distribution that includes more adolescents and adults.

Limitations

A strength of this report is the presentation of both survey and clinician interview data, which converge on the same conclusions. Regardless of the modality, however, retrospective reporting of skill attainment and loss carries the potential for telescoping (Hus et al., 2011) and limited concordance with systematic prospective observations and reports (Havdahl et al., 2023; Ozonoff & Iosif, 2019). While the current report constitutes the largest set of this type of phenotypic data reported for PMS, because of deidentification procedures, we cannot ascertain the degree of overlap in the samples for the studies. Although the samples in both studies were large, they are likely not an unbiased reflection of the PMS population. First, both studies enrolled participants with a known PMS diagnosis, and they may differ in systematic ways – most likely in increased severity -- from those who are not diagnosed. In fact, delayed milestones are more likely to trigger pediatric primary care physicians to refer young children for genetic testing (Srivastava et al., 2019). PMSIR participants were included if they responded to any portion of the developmental questionnaire; the resulting sample was 67% of eligible participants, and the response rate for individual items varied. It is possible that caregivers of individuals who had experienced a delay or loss were biased towards response to the form or particular items. While the sample size differed across DSC items, this was due to systematic study design changes, and does not likely reflect any response bias. Both samples lacked racial and ethnic diversity, thus limiting external validity. We also lack detailed enough genetic variant/deletion data in the registry to be able to include a detailed genotype-phenotype analysis. However, we direct readers to other work from the DSC documenting that loss of language skills, as well as greater attainment of language skills (i.e. single words and phrase speech) is significantly more common among people with small deletions (Class I) and sequence variants (Levy et al., 2022). Another limitation for a comprehensive understanding of skill loss in this population is that the measures focused almost exclusively on early developmental skills, which means that these results shed no light on later loss of more advanced skills. Finally, we were limited in our ability to compare or synthesize across studies by differences in data acquisition, such as how specific skills were defined and how age of acquisition was obtained (categories versus continuous). Future prospective study should

collect such detailed longitudinal data, facilitating the use of quantitative models for the development and loss of these important skills.

Conclusion

The current paper described results from two studies showing acquisition and loss of specific gross motor, fine motor, self-help, social and communication skills of individuals with PMS. Across studies, an overwhelming proportion of individuals with PMS were reported to be delayed in acquiring basic skills, validating several other studies reporting early and significant developmental delays in this condition. Skill loss/regression was also commonly reported across several types of developmental skills, including some after age 10, a result that is especially striking given recent reports of skill loss co-occurring with the onset of neuropsychiatric changes observed around puberty (Kohlenberg et al., 2020). Future research focused on prospective reporting of acquisition/loss of skills and subtle behavioral changes in childhood through young adulthood, with special attention to antecedents of these losses, will be valuable to further inform clinical practice in the care of individuals with PMS.

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Figure Legends

Figure 1. Parent-Reported Skill Attainment in the PMSIR. PMSIR = Phelan McDermid Syndrome International Registry. Figure depicts the cumulative percentage (vertical axis) of the sample (N=374) that had acquired a particular skill (labeled in order from highest percentage to lowest percentage) by each age response category (horizontal axis). The percentage is of valid responses, as the missing data and "Unsure" responses were excluded; the functional denominator ranged from 251 – 353 across domains (see Table 2).

Figure 2. Parent-Reported Skill Attainment in the DSC Natural History Study. DSC = Developmental Synaptopathies Consortium. Figure depicts the cumulative percentage (vertical axis) of the sample (N=207) that had acquired a particular skill (labeled in order from highest percentage to lowest total percentage) by each age response category (horizontal axis). During a clinical interview, the participants responded with age in months for skills in the language and motor domains, but these were categorized to facilitate comparison to the Phelan McDermid Syndrome International Registry. The functional denominator ranged from 70 – 203 across skills (see Table 4).

Table 1. Demographic Information

		PMSIR Survey	DSC Natural History
N		374	207
Age (years)[a]			
	Range	2.50 - 55.10	1.57 - 49.42
	Median	13.30	10.01
	IQR	9.70 - 20.40	6.54 - 17.42
Gender			
	Female	203 (54%)	86 (42%)
	Male	171 (46%)	114 (55%)
	Missing	0	7 (3%)
Race[b]			
	Asian	8 (2%)	14 (7%)
	Black (African American)	2 (1%)	5 (2%)
	Caucasian (Latino/Hispanic)	48 (13%)	NA
	Caucasian (Not Latino/Hispanic)	200 (53%)	NA
	Native American, American Indian, or Alaska Native	3 (1%)	1 (<1%)
	Other	45 (12%)	NA
	White	NA	164 (79%)
	Multiple	NA	7 (3%)
	Missing	68 (18%)	16 (8%)
Ethnicity[b]			
	Hispanic, Latino, or Spanish origin	NA	19 (9%)
	Not Hispanic, Latino, or Spanish origin	NA	173 (84%)
	Missing	NA	15 (7%)
Country[b]			
	United States	228 (61%)	NA
	Spain	27 (7%)	NA
	United Kingdom	23 (6%)	NA
	Australia	18 (5%)	NA
	Canada	16 (4%)	NA
	Brazil	12 (3%)	NA

France	10 (3%)	NA
Italy	10 (3%)	NA
Other	30 (8%)	NA

[a]Age was missing for one participant in the PMSIR sample. For the DSC sample, data from multiple visits were used. The oldest available age at which the participant had at least some acquisition data is recorded here.

[b]Categories are reported as they were shown to participants; these differed slightly across studies. NA indicates that the category was not used for that study.

Note: PMSIR = Phelan McDermid Syndrome International Registry; DSC = Developmental Synaptopathies Consortium; IQR = interquartile range.

Table 2. PMSIR Acquisition of Skills (N=374)

Domain	Skill	Missing Data n (% of total)	Skill Acquisition, n (%)			Age of Acquisition			Age (years) of Children Not Yet Acquired Skill
			No	*Yes*	*Yes, 95% CI*	*25th %ile*	*Median*	*75th %ile*	*Median [IQR]*
Communication	Social smile	59 (16%)	16 (5%)	299 (95%)	(92%, 97%)*	0 - 3 mos	4 - 7 mos	8 - 11 mos	13 [9, 18]
	Single syllable utterance	47 (13%)	62 (19%)	265 (81%)	(77%, 85%)	8 - 11 mos	12 - 18 mos	19 - 24 mos	12 [9, 18]
	First verbal word	62 (17%)	133 (43%)	179 (57%)	(52%, 63%)	12 - 18 mos	19 - 24 mos	31 - 36 mos	12 [7, 13]
	Verbal two word	56 (15%)	205 (64%)	113 (36%)	(30%, 41%)	25 - 30 mos	31 - 36 mos	4 - 5 yrs	12 [8, 16]
	Read whole words	61 (16%)	258 (82%)	55 (18%)	(13%, 22%)	4 - 5 yrs	6 - 7 yrs	8 - 9 yrs	12 [8, 16]
	Phonics-type reading	67 (18%)	284 (93%)	23 (7%)	(5%, 11%)*	6 - 7 yrs	8 - 9 yrs	8 - 9 yrs	12 [9, 18]
	Type with keyboard	59 (16%)	277 (88%)	38 (12%)	(8%, 16%)	6 - 7 yrs	8 - 9 yrs	10 yrs +	11 [8, 16]
Fine Motor	Look at, reach, grasp object	108 (29%)	9 (3%)	257 (97%)	(94%, 98%)*	4 - 7 mos	8 - 11 mos	12 - 18 mos	10 [7, 14]
	Transfer object / hands	123 (33%)	25 (10%)	226 (90%)	(86%, 93%)*	8 - 11 mos	12 - 18 mos	19 - 24 mos	10 [7, 13]
	Index finger point	98 (26%)	107 (39%)	169 (61%)	(55%, 67%)	12 - 18 mos	25 - 30 mos	31 - 36 mos	11 [8, 14]
	Clap hands	82 (22%)	82 (28%)	210 (72%)	(67%, 77%)	12 - 18 mos	19 - 24 mos	31 - 36 mos	11 [8, 13]
	Release object to container	103 (28%)	67 (25%)	204 (75%)	(70%, 80%)	12 - 18 mos	19 - 24 mos	31 - 36 mos	11 [8, 14]
	Hit two objects together	123 (33%)	71 (28%)	180 (72%)	(66%, 77%)	12 - 18 mos	19 - 24 mos	25 - 30 mos	10 [7, 13]
	Pincer grasp	103 (28%)	72 (27%)	199 (73%)	(68%, 79%)	12 - 18 mos	19 - 24 mos	31 - 36 mos	10 [6, 14]
	Hold/drink from cup	65 (17%)	130 (42%)	179 (58%)	(52%, 63%)	19 - 24 mos	31 - 36 mos	4 - 5 yrs	11 [7, 14]
	Turn knobs	100 (27%)	105 (38%)	169 (62%)	(56%, 67%)	25 - 30 mos	31 - 36 mos	4 - 5 yrs	11 [7, 13]
	Stack/balance blocks	84 (22%)	135 (47%)	155 (53%)	(48%, 59%)	19 - 24 mos	31 - 36 mos	4 - 5 yrs	11 [8, 15]
Gross Motor	Hold head up	68 (18%)	1 (0%)	305 (100%)	(98%, 100%)*	0 - 3 mos	4 - 7 mos	8 - 11 mos	12 [7, 16]
	Roll over back/stomach	67 (18%)	12 (4%)	295 (96%)	(93%, 98%)*	4 - 7 mos	4 - 7 mos	8 - 11 mos	10 [7, 12]
	Sit when placed	50 (13%)	20 (6%)	304 (94%)	(91%, 96%)*	4 - 7 mos	8 - 11 mos	12 - 18 mos	13 [13, 13]
	Crawl hands/knees	43 (11%)	72 (22%)	259 (78%)	(74%, 83%)	8 - 11 mos	8 - 11 mos	12 - 18 mos	11 [8, 16]
	Walk unassisted	21 (6%)	63 (18%)	290 (82%)	(78%, 86%)	12 - 18 mos	19 - 24 mos	25 - 30 mos	11 [9, 12]
	Climbs stairs standing	62 (17%)	105 (34%)	207 (66%)	(61%, 72%)	19 - 24 mos	31 - 36 mos	4 - 5 yrs	8 [6, 12]
	Descend stairs	67 (18%)	117 (38%)	190 (62%)	(56%, 67%)	25 - 30 mos	31 - 36 mos	4 - 5 yrs	11 [8, 14]
	Jump/both feet	63 (17%)	177 (57%)	134 (43%)	(38%, 49%)	31 - 36 mos	4 - 5 yrs	4 - 5 yrs	10 [7, 12]
	Pedal tricycle	42 (11%)	196 (59%)	136 (41%)	(36%, 46%)	31 - 36 mos	4 - 5 yrs	6 - 7 yrs	9 [6, 12]
Self Help	Undress	173 (46%)	56 (28%)	145 (72%)	(66%, 78%)	3 - 4 yrs	5 - 6 yrs	7 - 8 yrs	11 [7, 18]

Dress	196 (52%)	87 (49%)	91 (51%)	(44%, 58%)	3 - 4 yrs	7 - 8 yrs	9 - 10 yrs	11 [7, 17]
Toilet independently/day	193 (52%)	87 (48%)	94 (52%)	(45%, 59%)	3 - 4 yrs	5 - 6 yrs	9 - 10 yrs	6 [5, 12]
Toilet-trained/night	212 (57%)	94 (58%)	68 (42%)	(34%, 50%)	3 - 4 yrs	7 - 8 yrs	9 - 10 yrs	8 [6, 11]
Drink	138 (37%)	16 (7%)	220 (93%)	(89%, 96%)*	1 - 2 yrs	3 - 4 yrs	5 - 6 yrs	12 [7, 17]
Feed self	89 (24%)	19 (7%)	266 (93%)	(90%, 96%)*	1 - 2 yrs	3 - 4 yrs	3 - 4 yrs	10 [6, 13]

*Clopper-Pearson exact method

Note: PMSIR = Phelan McDermid Syndrome International Registry; CI = confidence interval; IQR = interquartile range; mos = months; yrs = years; IQR. Confidence intervals were calculated using the normal approximation was used unless n(1-p) or n(p) was less than 5, or p or 1-p was less than .10, in which case the Clopper-Pearson exact method was used. For all items, a choice of “Unsure” was recoded as missing. Age of acquisition is summarized using the quantiles of the ordinal response categories, after those who selected Unsure or Not Applicable (or whose data were missing) were excluded. For Communication, Fine Motor, and Gross Motor domains, the response options were: 0 - 3 months, 4 - 7 months, 8 - 11 months, 12 - 18 months, 19 - 24 months, 25 - 30 months, 31 - 36 months, [note that no 37 – 48 month category was provided as an option], 4 - 5 years, 6 - 7 years, 8 - 9 years, 10 years +. For Self Help, the response options were: 1 - 2 years old, 3 - 4 years old, 5 - 6 years old, 7 - 8 years old, 9 - 10 years old, Over 10 years old. These acquisition rates/ages are illustrated in Figure 1.

Table 3. PMSIR Loss of Skills (N=374)

Item	Response	Fine Motor Skills	Gross Motor Skills	Self-Help Skills	Social Skills
		n (%)	***n (%)***	***n (%)***	***n (%)***
Loss of Skills	No	194 (61%)	214 (62%)	230 (67%)	248 (76%)
	Yes	123 (39%)	129 (38%)	114 (33%)	77 (24%)
	Yes, 95% CI	[33%,44%]	[32%,43%]	[28%,38%]	[19%,28 %]
	Unsure	*37*	*29*	*19*	*38*
	Missing	*20*	*2*	*11*	*11*
		n (% of those with loss)	***n (% of those with loss)***	***n (% of those with loss)***	***n (% of those with loss)***
Age of Loss	1 - 2 years old	37 (35%)	39 (35%)	18 (18%)	23 (32%)
	3 - 4 years old	30 (29%)	34 (30%)	30 (30%)	16 (22%)
	5 - 6 years old	12 (11%)	7 (6%)	8 (8%)	6 (8%)
	7 - 8 years old	2 (2%)	4 (4%)	7 (7%)	4 (5%)
	9 - 10 years old	2 (2%)	3 (3%)	3 (3%)	2 (3%)
	Over 10 years old	22 (21%)	25 (22%)	33 (33%)	22 (30%)
	Unsure	*15*	*9*	*8*	*3*
	Missing	*3*	*8*	*7*	*1*
Regain after Loss	No	38 (32%)	40 (33%)	37 (34%)	28 (38%)
	Partially	48 (41%)	46 (38%)	44 (40%)	28 (38%)
	Yes	32 (27%)	36 (30%)	29 (26%)	18 (24%)
	Unsure	*2*	*1*	*2*	*1*
	Missing	*3*	*6*	*2*	*2*

Note: PMSIR = Phelan McDermid Syndrome International Registry; CI = confidence interval using the normal approximation. Loss was queried at the domain level rather than at the skill level. Response categories are reproduced exactly as they appeared in the questionnaire; Unsure and Missing were both treated as missing data and excluded from calculation of percentages.

Table 4. DSC Acquisition of skills (N=207)

Domain	Skill	Sources		Acquired Skill			Skill Not Acquired	
			Respondents	*n (%)*	*95% CI*	*Acquisition age in months, median [IQR]*	*n (%)*	*Current age in years, median [IQR]*
Language	babbled	BC	115	88 (77%)	(69%, 84%)	9 [6, 15]	27 (23%)	9 [7, 15]
	words	AC	196	131 (67%)	(60%, 73%)	24 [15, 36]	65 (33%)	6 [3, 10]
	phrases	AC	197	89 (45%)	(38%, 52%)	36 [24, 60]	108 (55%)	6 [4, 10]
	fluent	C	72	22 (31%)	(20%, 41%)	60 [42, 66]	50 (69%)	10 [6, 18]
Motor	reach	BC	114	112 (98%)	(94%, 100%)*	1 [1, 9]	2 (2%)	12 [10, 14]
	rolling	BC	119	115 (97%)	(92%, 99%)*	6 [4, 9]	4 (3%)	9 [6, 13]
	sitting with support	B	77	73 (95%)	(87%, 99%)*	8 [6, 10]	4 (5%)	7 [7, 8]
	sitting alone	BC	128	122 (95%)	(90%, 98%)*	9 [7, 12]	6 (5%)	7 [6, 9]
	crawling	BC	128	109 (85%)	(79%, 91%)	10 [9, 12]	19 (15%)	9 [7, 13]
	pull to stand	B	84	77 (92%)	(84%, 97%)*	14 [11, 24]	7 (8%)	7 [6, 11]
	walk alone	ABC	203	188 (93%)	(88%, 96%)*	17 [14, 23]	15 (7%)	3 [2, 5]
Self-Help	hold bottle	B	70	58 (83%)	(74%, 92%)	12 [8, 18]	12 (17%)	7 [6, 15]
	bladder	C	74	30 (41%)	(29%, 52%)	55.5 [42, 60]	44 (59%)	10 [7, 18]
	bowel	C	75	28 (37%)	(26%, 48%)	52 [36, 67.5]	47 (63%)	10 [6, 18]
						Acquired by 12 months, n (%)		
Social	smiles	BC	138	122 (88%)	(83%, 94%)	96 (70%)	16 (12%)	8 [7, 10]
	eye contact	BC	137	108 (79%)	(72%, 86%)	76 (55%)	29 (21%)	9 [7, 17]
	responds	BC	140	129 (92%)	(86%, 96%)*	64 (46%)	11 (8%)	7 [4, 10]
	shows	BC	135	69 (51%)	(43%, 60%)	25 (19%)	66 (49%)	9 [7, 14]
	points	BC	138	74 (54%)	(45%, 62%)	25 (18%)	64 (46%)	9 [7, 17]
	waves	BC	136	68 (50%)	(42%, 58%)	26 (19%)	68 (50%)	9 [6, 13]

*Clopper-Pearson exact method

Note: DSC = Developmental Synaptopathies Consortium; CI = confidence interval; IQR = interquartile range. Confidence intervals were calculated using the normal approximation was used unless n(1-p) or n(p) was less than 5, or p or 1-p was less than .10, in which case the Clopper-Pearson exact method was used. Data were combined across four forms (Sources: A = Autism Diagnostic Interview-Revised and Baseline Developmental

History, B = Regression Supplement, C = Early Skills Attainment and Loss form) and the latest available response was used for each skill (see Methods). The sample size for each skill is indicated in the Respondents column.

Table 5. DSC Loss of skills (N=207)

Domain	Skill	Respondents	Missing Data	Skill Lost			Skill Not Lost	
			n (% of acquired)	*n (%)*	*95% CI*	*Age of loss in months, median [IQR]*	*n (%)*	*Current age in years, median [IQR]*
Language	babbled	84	4 (5%)	35 (42%)	(31%, 52%)	18 [12, 29]	49 (58%)	10 [7, 16]
	words	54	77 (59%)	26 (48%)	(35%, 61%)	27 [20, 78]	28 (52%)	13 [10, 17]
	phrases	35	54 (61%)	12 (34%)	(19%, 50%)	60 [23, 105]	23 (66%)	13 [10, 18]
	fluent	21	1 (5%)	4 (19%)	(5%, 42%)*	156 [132, 249]	17 (81%)	13 [12, 16]
Motor	reach	110	2 (2%)	6 (5%)	(2%, 11%)*	20 [14, 46]	104 (95%)	9 [7, 17]
	rolling	113	2 (2%)	4 (4%)	(1%, 9%)*	13 [6, 23]	109 (96%)	9 [7, 17]
	sitting with support	71	2 (3%)	1 (1%)	(0%, 8%)*	18 [18, 18]	70 (99%)	9 [7, 13]
	sitting alone	120	2 (2%)	2 (2%)	(0%, 6%)*	233 [122, 345]	118 (98%)	9 [7, 16]
	crawling	106	3 (3%)	2 (2%)	(0%, 7%)*	14 [13, 14]	104 (98%)	9 [7, 15]
	pull to stand	74	3 (4%)	0	(0%, 5%)*	NA	74 (100%)	9 [7, 12]
	walk alone	128	60 (32%)	5 (4%)	(1%, 9%)*	54 [42, 300]	123 (96%)	9 [7, 16]
Self-Help	hold bottle	58	0 (0%)	2 (3%)	(0%, 12%)*	35 [25, 44]	56 (97%)	9 [8, 12]
	bladder	30	0 (0%)	10 (33%)	(16%, 50%)	144 [108, 185]	20 (67%)	13 [9, 20]
	bowel	27	1 (4%)	4 (15%)	(4%, 34%)*	258 [171, 339]	23 (85%)	13 [12, 19]
Social	smiles	120	2 (2%)	23 (19%)	(12%, 26%)	24 [18, 35]	97 (81%)	9 [7, 16]
	eye contact	105	3 (3%)	18 (17%)	(10%, 24%)	25 [17, 32]	87 (83%)	9 [7, 17]
	responds	125	4 (3%)	25 (20%)	(13%, 27%)	24 [16, 48]	100 (80%)	9 [7, 16]
	shows	66	3 (4%)	9 (14%)	(5%, 22%)	33 [24, 39]	57 (86%)	11 [8, 18]
	points	72	2 (3%)	15 (21%)	(11%, 30%)	36 [24, 51]	57 (79%)	9 [7, 14]
	waves	67	1 (1%)	18 (27%)	(16%, 37%)	36 [20, 90]	49 (73%)	10 [7, 16]

*Clopper-Pearson exact method

Note: DSC = Developmental Synaptopathies Consortium; CI = confidence interval; IQR = interquartile range. Confidence intervals were calculated using the normal approximation was used unless n(1-p) or n(p) was less than 5, or p or 1-p was less than .10, in which case the Clopper-Pearson exact method was used. Data were combined across two forms (Regression Supplement and Early Skills Attainment and Loss form). The sample

size for each skill is indicated in the Respondents column. Missing data refers to participants who were reported to have acquired the skill, but for whom loss information was not reported. The high rate of missing data for major milestones (walking, words, phrases) is because much of the acquisition data for these skills came from the Autism Diagnostic Interview-Revised, which does not explicitly ask about loss of these milestones (loss items are for language, not split by words and phrases, and for skills generally).

Figure1

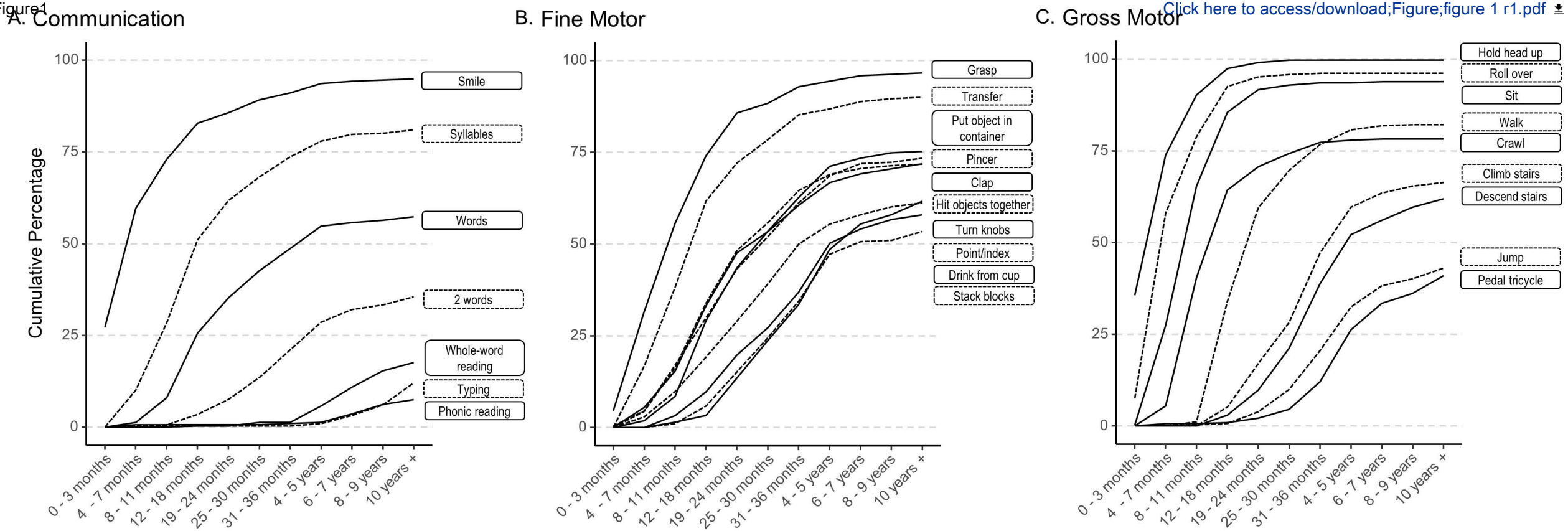

Figure2