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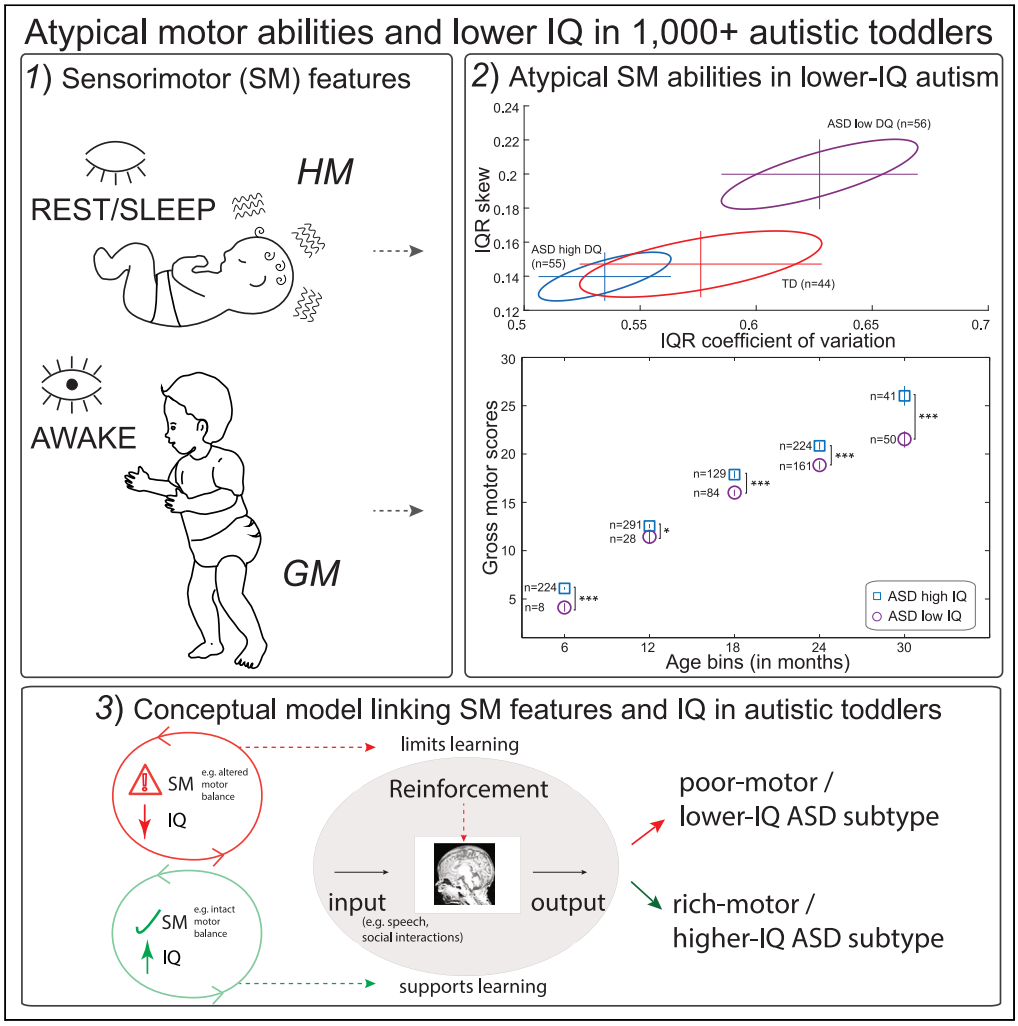

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Highlights

Atypical sensorimotor features associate with lower IQ in 1,000 autistic toddlers

Higher IQ in autism confers resilience, associating with typical motor features

Poorer sensorimotor functioning is a key feature of lower-IQ early childhood autism

Findings have implications for individualized interventions for subtypes of autism

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Sensorimotor variability distinguishes early features of cognition in toddlers with autism

Kristina Denisova[1,3,*] and Daniel M. Wolpert[2]

SUMMARY

The potential role of early sensorimotor features to atypical human cognition in autistic children has received surprisingly little attention given that appropriate movements are a crucial element that connects us to other people. We examined quantitative and observation-based movements in over 1,000 toddlers diagnosed with autism spectrum disorder (ASD) with different levels of cognitive abilities (intelligence quotient, IQ). Relative to higher-IQ ASD toddlers, those with lower-IQ had significantly altered sensorimotor features. Remarkably, we found that higher IQ in autistic toddlers confers resilience to atypical movement, as sensorimotor features in higher-IQ ASD children were indistinguishable from those of typically developing healthy control toddlers. We suggest that the altered movement patterns may affect key autistic behaviors in those with lower intelligence by affecting sensorimotor learning mechanisms. Atypical sensorimotor functioning is a key feature in lower-IQ early childhood autism. These findings have implications for the development of individualized interventions for subtypes of autism.

INTRODUCTION

An outstanding question of tremendous scientific significance is the neurobiology that gives rise to autism spectrum disorders (ASDs) in children. A crucial element that connects us to other people is our ability to generate appropriate movements. In early infancy, movements allow newborns to look around for their mother using eye gaze, head, or body turns, so that they can share with the mother interesting things that they see. Over time we build a rich repertoire of sensorimotor actions that become integrated with attention, cognition, and memory systems as mind and brain development unfolds, and these abilities support our successful interactions with those around us. A substantial body of work in neurotypical healthy adults has cemented the importance of how sensorimotor experience affects the way our brains form and express motor memories[1] and how such experience determines the movements that we can generate.[2,3] Moreover, it is known that modifying the variability of movement is a key component of successful motor planning.[4,5] While some motor variability is beneficial in that it allows exploration thereby enhancing motor learning,[6,7] excess variability can inhibit learning.[8,9] The central importance of early sensorimotor integrity for higher-level cognitive capacities has also been demonstrated in healthy human infants; for example, temporary sensorimotor impairment impedes speech perception during wakefulness in 6 month-old infants during a critical period for first language acquisition.[10] Further, convergent evidence points to the overall significance of sensorimotor development for normative development in human infants[11,12] and infant rats, particularly during sleep.[13,14]

Here, we investigate the relation between early sensorimotor features and cognition in toddlers who were later diagnosed with ASD. While lower intelligence quotient (IQ) scores in infancy are predictive of future ASD diagnoses in childhood,[15] not all children with ASD have lower cognitive abilities in infancy. As such, the early features that may distinguish ASD children with "lower" vs. "higher" cognitive abilities are of great research and clinical interest. Despite the necessity to discover features that are part and parcel of cognitive differences in children with autism,[16,17] this knowledge is still lacking in children before they receive ASD diagnosis.

Important insights on altered sensorimotor movements during sleep and lower cognitive skills have been obtained by quantitative studies with 1–2 month-old infants at a high familial likelihood[18] or risk for autism (HL: older biological sibling with ASD) compared to those at low likelihood or risk (LL).[19] Moreover, atypical sensorimotor functioning during wakefulness has been detected in older children and adults already diagnosed with ASD.[20] However, little is known about sensorimotor deficits in infants from the population at large who go on to receive ASD diagnoses in early childhood.

Of note, the targeted lower bound age (12 months) for our study is near the time point (9–10 months) at which atypical movement signatures during sleep were previously established in HL (vs. LL) infants who had confirmed ASD diagnoses at 36 months.[21] A great deal of time during the first 2–3 years of life is spent in sleep (up to 50% or about 12 h of each day[22]). During sleep, twitches, or sudden movements are common and contribute to normal development.[14] Atypical sensorimotor functioning during this unique period may amplify potential

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cognitive anomalies. More broadly, early learning is supported during sleep.[23,24] Further, sleep difficulties in children with ASD[25] (cf. studies of Richdale[26] and Sivertsen et al.[27]), as well as associations between sleep and cognition in ASD,[28,29] have now been firmly established.

If early sensorimotor features were shown to be correlated with differences in early cognition in some children *before* they are diagnosed with an ASD, then this would be an important component to understand the nature of mind and brain development in children with autism. Atypical sensorimotor development may affect early cognition, or vice versa; or both might be markers of the same underlying, but unknown, factor.

Here, we note that the ongoing rs-fcMRI and fMRI studies approach the importance of sensorimotor features from a different perspective.[30] Because head movements affect the acquired blood oxygenation-level dependent (BOLD) signal,[31] during analyses researchers routinely edit out (or regress out) s BOLD data time points showing heightened head movements, as for these studies head movements are a nuisance and considered a random occurrence during an MRI scan session. In contrast, the current study directly focuses on this head motion rather than the BOLD signal. Specifically, an alternative position is that head movements in young children represent important neurophysiological features of the developing nervous system functioning and brain development.

We designed two sets of analyses in order to probe rigorously the relation between movement and cognitive abilities in toddlers *prior* to their ASD diagnoses, during sleep and during wakefulness. In our first set of analyses, we assess motor system characteristics in 202 autistic and neurotypical toddlers (mean age: 30 months; ASD or neurotypical development ascertained by 3 years) undergoing (MRI) scans acquired during natural sleep. Movement time series are obtained in an automatic manner from Statistical Parametric Mapping (SPM),[32,33] and robust measures of the variability of sensorimotor features (the coefficient of variance and skewness of the distribution of the infants' angular head speeds) are quantified. We tested whether ASD toddlers (N = 111) grouped by different levels of verbal, non-verbal, and overall cognitive abilities based on the direct observation of the toddlers' responses during the Mullen Scales of Early Learning (MSEL) assessment also differ on sensorimotor features. We further tested whether ASD toddlers with higher cognitive abilities have different or similar sensorimotor features relative to neurotypical children from the same cohort (N = 91), including those who are healthy controls, those who are younger siblings of children with autism, and those with previous developmental concerns. (Comparisons focus on higher-IQ ASD children because of the substantially different distribution of IQ scores among ASD and TD children[15]; see STAR Methods.).

Our second set of analyses aimed to increase the generalizability of the findings associating cognitive abilities with sensorimotor features in autistic children. Are altered sensorimotor features present primarily during sleep, or is there also evidence for the association between sensorimotor alterations and impaired cognitive abilities during wakefulness, and before children are diagnosed with autism? To address this key question, we examined the association between general motor skills (using an observational measure compared to our objective, quantitative measures in the scanner described previously) and levels of cognitive abilities in a very large, independent sample of over 1,000 infants and toddlers assessed on motor abilities during wakefulness at 6, 12, 18, 24, and 30 months. As in the main sample, children received ASD diagnoses by 3–4 years.

Overall, we hypothesized that those ASD children with lower IQ will also have altered movement during sleep relative to those with higher IQ. We further hypothesized that lower motor skills during wakefulness may be detected in lower-IQ children with ASD, relative to those with higher IQ.

RESULTS

We computed statistical features for each toddler's movements individually, and then performed group-level statistics. We focus on two measures of movement which are independent of overall speed: coefficient of variation and skewness of the head speed angular rotation (see STAR Methods). The coefficient of variation (standard deviation of speed divided by mean speed) is a measure of movement variability whereas skewness of the distribution of speed measures asymmetry in the speed distribution relative to the mean speed (positive values have skewness toward higher speeds). Figure 1 shows three examples which vary in these measures. We next report findings from the main sample of toddlers with ASD (Sample #1), with movement data acquired during natural sleep; we compare a higher-IQ ASD subgroup to 3 groups of toddlers from the same cohort who have neurotypical outcomes and average or above-average IQ. The last section presents findings on motor features and IQ from an independent sample of infants and toddlers with ASD (Sample #2), in which motor skills were assessed during wakefulness.

Significant sensorimotor alterations during sleep in lower-IQ vs. higher IQ toddlers with ASD

We designed the first set of analyses to test whether ASD toddlers grouped by different levels of cognitive ability also differ on sensorimotor features assessed during sleep. We asked if sensorimotor statistical features of toddlers with ASD differ between those with lower IQ and higher IQ (all t tests were two-tailed and we also present Bayes Factor (BF) analyses).

We find that ASD toddlers with lower full-scale developmental quotient (DQ) have altered sensorimotor features on both parameters. Specifically, we detected significantly greater skewness in ASD toddlers with lower DQ relative to those with higher DQ ($t(109) = 2.396$, $p = 0.018$; BF: 2.55), and greater although not significantly different, coefficient of variation (c.o.v) ($t(109) = 1.807$, $p = 0.073$; BF: 0.86) (Figure 2A). Of note, the patterns identified in the subgrouping analysis hold when we considered cognitive ability as a continuous construct, computing non-parametric Spearman's correlation between each of the parameters and DQ: (c.o.v. r_s (109) = −0.15, $p = 0.119$; skew r_s (109) = −0.22, $p = 0.020$) (Figures S1A and S2A).

Importantly, we find that the result of differences in the sensorimotor features of lower-DQ vs. higher-DQ ASD toddlers holds for both parameters when we repeated analyses excluding a small number of high likelihood infants, that is those with an older biological sibling

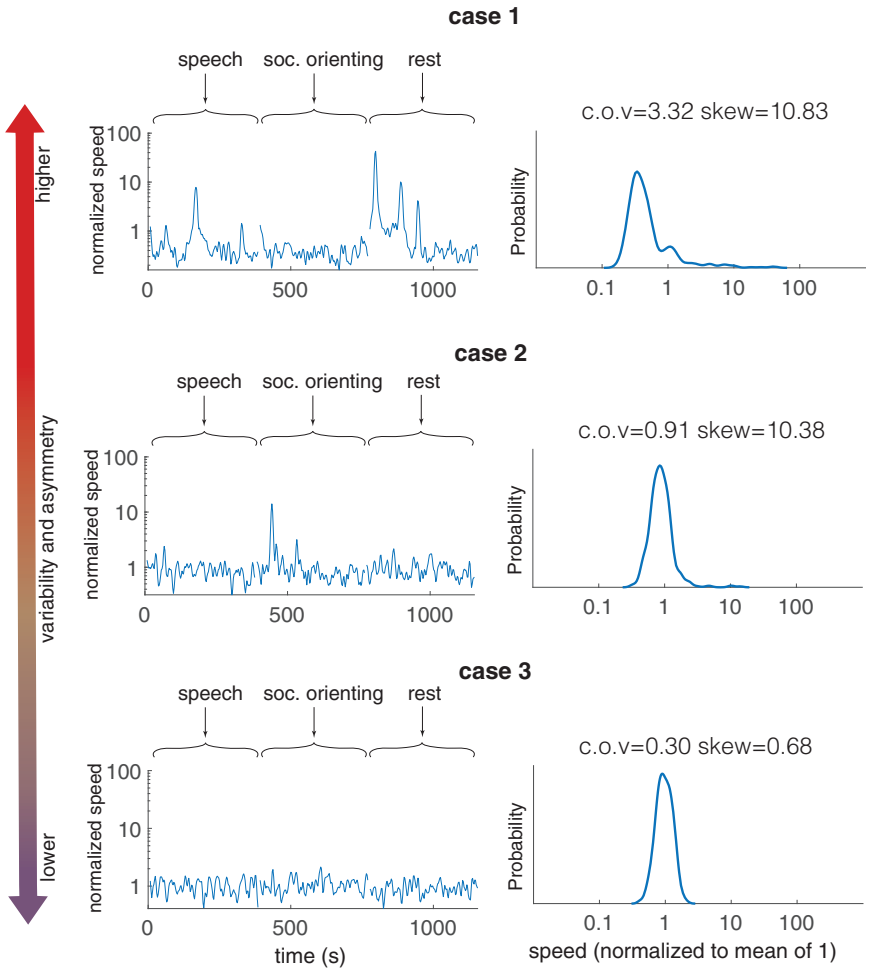

Figure 1. Illustration of how movements during sleep of individual autism spectrum disorder (ASD) cases (1–3) vary along the coefficient of variation (c.o.v) and skewness measures

The top panel shows a case (#1) characterized by a high c.o.v. (a measure of movement variability: standard deviation of speed divided by mean speed) as well as high skewness of the distribution of speed (a measure of asymmetry in the speed distribution; positive values have skewness toward higher speeds). The bottom panel shows a case (#3) characterized by both low c.o.v. and skewness (the middle panel illustrates a case (#2) midway between the two extremes).

already diagnosed with ASD (total N without HL infants: N = 105; c.o.v. BF = 1.18; skewness BF = 3.15; Figure S3A). Further, findings are consistent when data were analyzed separately by males and females (Figures S7 and S8); significant differences on both parameters were detected in the males-only lower-DQ vs. higher-DQ group. In particular, relative to the main comparison group for DQ, BF increased more than 10-fold for skewness (from BF = 2.55 to BF = 34.85) in the males-only group, providing strong evidence that lower DQ is associated with greater skewness for autistic toddlers who are boys (BF for the c.o.v. more than doubled; from BF = 0.86 to BF = 2.46; Figure S7).

This finding establishes for the first time that unlike higher-DQ ASD toddlers, those with lower-DQ have sensorimotor movements during sleep characterized by more variability (i.e., higher c.o.v.) and more asymmetry (i.e., skewed to higher speeds). Importantly, this finding is consistent for the Early Learning Composite (ELC), the standard score on the Mullen. ASD toddlers with lower ELC have a significantly greater skewness relative to those with higher ELC (t(109) = 2.313, p = 0.023; BF: 2.16) but similar c.o.v. (t(109) = 1.261, p = 0.209; BF: 0.41) (Figure 2B). (Spearman's correlation between each of the parameters and ELC: c.o.v. r_s (109) = −0.13, p = 0.161; skew r_s (109) = −0.21, p = 0.027; Figures S1B and S2B).

We sought to verify whether altered sensorimotor features and lower IQ are evident for the subdomain estimates of IQ in these ASD toddlers. ASD toddlers with lower verbal IQ (VIQ) have a significantly greater skewness relative to those with higher VIQ (t(109) = 2.097, p = 0.038; BF: 1.42) but similar c.o.v. (t(109) = 1.185, p = 0.238; BF: 0.38) (Figure 2C). (Spearman's correlation between each of the parameters and VIQ: skew r_s (109) = −0.21, p = 0.025; c.o.v. r_s (109) = −0.14, p = 0.148; Figures S1C and S2C).

With regard to performance (non-verbal) IQ, we find that relative to ASD toddlers with higher PIQ, those with lower PIQ have greater, although not significantly different, c.o.v. (t(109) = 0.309, p = 0.757; BF: 0.21) and skewness (t(109) = 1.264, p = 0.209; BF: 0.41) (Figure 2D).

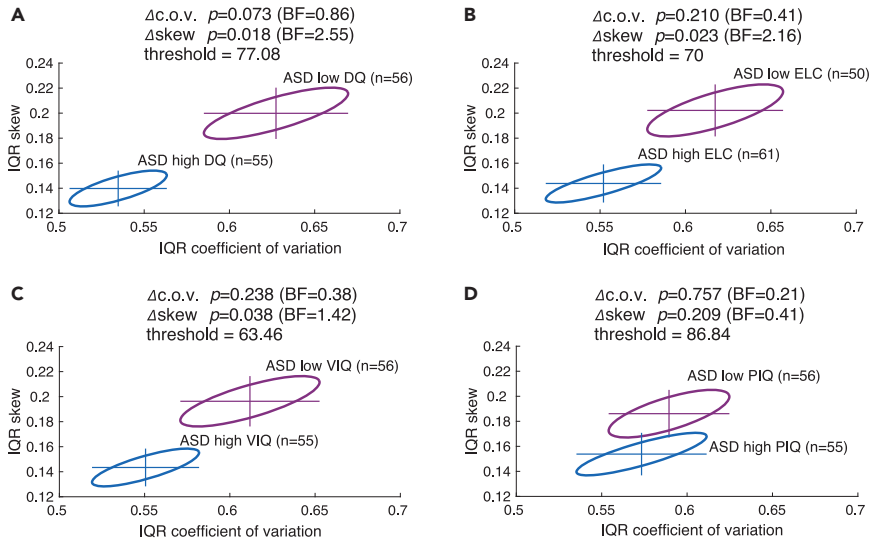

Figure 2. Altered sensorimotor features during sleep in toddlers with autism spectrum disorder (ASD) who have lower cognitive abilities

Panels show group means of skewness of head speed distribution plotted against coefficient of variance of head speed. Ellipses show standard error of the mean with lines showing cardinal standard errors. In the titles we report *p* values for statistical tests comparing the difference in the measures across the two groups, that is H_0: Δ c.o.v = 0 and H_0: Δ skewness = 0, and report Bayes Factor (BF) corresponding to each comparison. Panel subgroupings (lower vs. higher IQ) based on (A) full-scale Developmental Quotient (DQ), (B) full-scale Early Learning Composite (ELC) standard score, (C) verbal IQ (VIQ), and (D) performance IQ (PIQ). Results (higher- vs. lower-IQ ASD) for DQ: skew, (t(109) = 2.396, p = 0.018; BF: 2.55; c.o.v., (t(109) = 1.807, p = 0.073; BF: 0.86; for ELC: skew, t(109) = 2.313, p = 0.023; BF: 2.16; c.o.v., t(109) = 1.261, p = 0.209; BF: 0.41; for VIQ: skew, t(109) = 2.097, p = 0.038; BF: 1.42; c.o.v., t(109) = 1.185, p = 0.238; BF: 0.38; for PIQ: skew, t(109) = 1.264, p = 0.209; BF: 0.41; c.o.v., t(109) = 0.309, p = 0.757; BF: 0.21. *Note*: IQ, Intelligence Quotient; BF: Bayes Factor.

(Spearman's correlation between each of the parameters and PIQ: c.o.v. r_s (109) = −0.09, p = 0.314; skew r_s (109) = −0.16, p = 0.080; Figures S1D and S2D).

Taken together, these findings in the ASD group establish that the nature of early sensorimotor features during sleep is significantly associated with the integrity of early cognitive abilities in ASD toddlers. Notably, these patterns were again consistent for ELC, VIQ, and PIQ comparisons when analyses were repeated without HL infants: Figures S3B–S3D.) Findings were consistent when data were analyzed separately by each of the 3 scanning conditions (speech, social orienting, and resting-state fMRI scans) (Figures S4–S6). Further, findings were consistent for these comparisons when data were analyzed separately by males and females (Figures S7 and S8). In particular, a key comparison of VIQ revealed an altered skewness parameter in children with lower-vs. higher-VIQ, within males-only (BF = 6.13) as well as within females-only (BF = 1.49) subgroupings.

Additional features characterizing lower-vs. higher-IQ ASD toddlers

Post-hoc, we examined additional features of lower-IQ vs. higher-IQ ASD subgroupings broken down using the standard IQ composite score (ELC) (below and above 70). Lower-ELC autistic children have higher autistic manifestations (i.e., higher or worse Calibrated Severity Scores (CSS)) on the ADOS relative to higher-ELC autistic children. The between-group differences are significant for Total CSS and Social Affect (SA) CSS scores. Specifically, Total CSS scores were significantly lower for those with lower IQ, t(109) = 2.534, p = 0.013; SA CSS scores were significantly lower for those with lower IQ, t(109) = 2.221, p = 0.028 (Restricted and Repetitive Behaviors (RRB) scores were similar: t(109) = 1.129, p = 0.262). (These findings were consistent for Spearman's correlations (Total CSS: r_s (109) = −0.2268, p = 0.0167; SA CSS r_s (109) = −0.2061, p = 0.0300; RRB CSS r_s (109) = −0.1775, p = 0.0624).).

Lower-ELC autistic children also have lower adaptive functioning scores on the Vineland Adaptive Behavior Scales-II (VABS-II) relative to higher-ELC autistic children. These between-group differences are significant for the standard composite ABC score and subdomain scores. Specifically, ABC scores were significantly lower for those with lower ELC, t(109) = −6.7014, p = 9.4324e-10; Communication (COMM) scores were significantly lower for those with lower ELC, t(109) = −5.7610, p = 7.8452e-08; Living (LIV) skills scores were significantly lower for those with lower ELC, t(109) = −4.7230, p = 6.9649e-06; Socialization (SOC) skills scores were significantly lower for those with lower ELC, t(109) = −5.1598, p = 1.1181e-06; Motor (MOT) skills scores were significantly lower for those with lower ELC, t(109) = −4.6155, p = 1.0768e-05. (These findings were consistent for Spearman's correlations [ABC score: r_s (109) = 0.6666, p = 1.4016e-15; COMM score: r_s (109) = 0.6227, p = 2.9344e-13; LIV score: r_s (109) = 0.5052, p = 1.5648e-08; SOC score: r_s (109) = 0.5351, p = 1.4477e-09; MOT score: r_s (109) = 0.4438, p = 1.0648e-06]).

Sensorimotor features during sleep in higher-IQ ASD vs. 3 neurotypical groups

It is important to establish whether the higher-IQ ASD subgroup differs from children with neurotypical outcomes in terms of the sensorimotor measures. Because heterogeneity might be present within "typically developing" children with average IQ, we compared the higher-IQ ASD

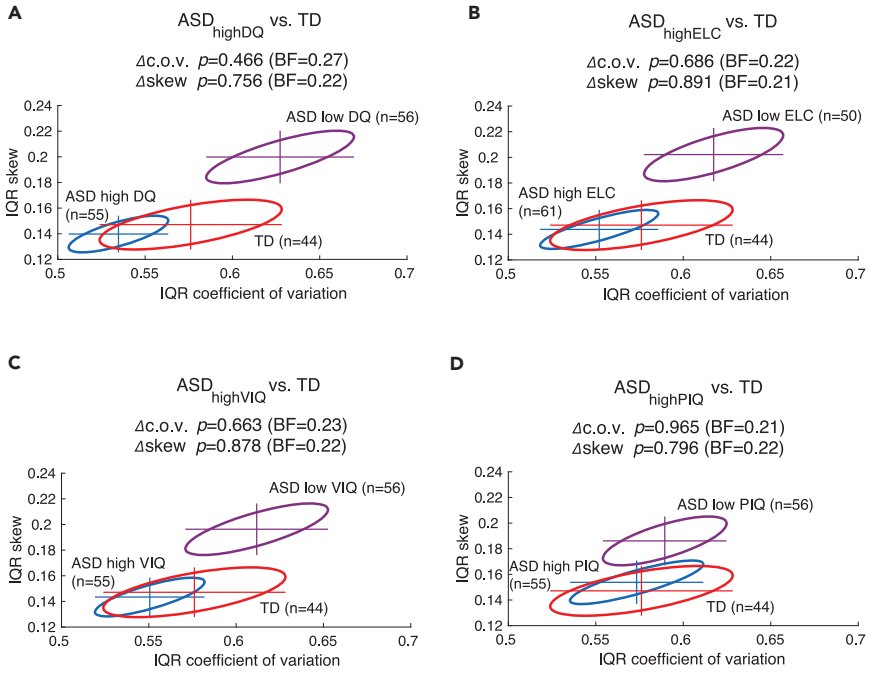

Figure 3. Sensorimotor features of neurotypical, typically developing (TD) healthy control toddlers are shown with toddlers with autism spectrum disorder (ASD) who have lower or higher cognitive abilities

The TD group is characterized by average or above average IQ, absence of familial autism risk and no previous or concurrent delays; TD group's sensorimotor features overlap those of the higher-IQ ASD group. Plotted as in Figure 2. (Ellipses show standard error of the mean with lines showing cardinal standard errors.) Panel subgroupings based on (A) full-scale Developmental Quotient (DQ), (B) full-scale Early Learning Composite (ELC) standard score, (C) verbal IQ (VIQ), and (D) performance IQ (PIQ). Results (higher-IQ ASD vs. TD) for DQ: skew, t(97) = 0.311, $p = 0.756$; BF: 0.22; c.o.v., t(97) = 0.732, $p = 0.466$; BF: 0.27; ELC: skew, t(103) = 0.136, $p = 0.891$; BF: 0.21; c.o.v., t(103) = 0.405, $p = 0.686$; BF: 0.22; VIQ: skew, t(97) = 0.153, $p = 0.878$; BF: 0.22; c.o.v., t(97) = 0.437, $p = 0.663$; BF: 0.23; PIQ: skew, t(97) = −0.259, $p = 0.796$; BF: 0.22; c.o.v., t(97) = 0.044, $p = 0.965$; BF: 0.21. *Note*: IQ, Intelligence Quotient; BF: Bayes Factor.

subgroup to *3 distinct groups with neurotypical outcomes*. We made comparisons to (*i*) a group of neurotypical developing healthy control toddlers (TDs); this group had no latent genetic likelihood or risk for autism due to a biological older sibling with ASD and no previous or current developmental or other (e.g., behavioral) concerns, (*ii*) to a group of neurotypical developing toddlers with an older biological sibling with ASD (SIB); this group was ascertained to be developing typically, but has a latent genetic risk for autism, and (*iii*) to a group of neurotypical developing toddlers who previously failed a screening at a pediatrician's office (FA); while children in this group are also ascertained to have typical development, they were previously identified as having potential developmental concerns in early infancy. All three neurotypical groups have average or above-average IQ (STAR Methods), and no toddlers within these groups have a full-scale IQ score (DQ or ELC) 2 SD below the mean.

Relative to neurotypical TD healthy controls with neither genetic risk for autism nor any previous or current developmental concerns, we found that higher-DQ ASD toddlers have similar c.o.v. (t(97) = 0.732, $p = 0.466$; BF: 0.27) and similar skewness (t(97) = 0.311, $p = 0.756$; BF: 0.22). These patterns are confirmed for ELC, VIQ, and PIQ. Relative to TD, higher-ELC ASD toddlers have similar c.o.v. (t(103) = 0.405, $p = 0.686$; BF: 0.22) and similar skewness (t(103) = 0.136, $p = 0.891$; BF: 0.21); higher-VIQ ASD toddlers have similar c.o.v. (t(97) = 0.437, $p = 0.663$; BF: 0.23) and similar skewness (t(97) = 0.153, $p = 0.878$; BF: 0.22); higher-PIQ ASD toddlers have similar c.o.v. (t(97) = 0.044, $p = 0.965$; BF: 0.21) and similar skewness (t(97) = −0.259, $p = 0.796$; BF: 0.22) (Figures 3A–3D).

In contrast, relative to typically developing SIB toddlers, we detected significantly lower c.o.v. (t(78) = 2.036, $p = 0.045$; BF: 1.43) and a significantly lower skewness (t(78) = 2.810, $p = 0.006$; BF: 6.66) in higher-DQ ASD toddlers (Figure 4A). Relative to the SIB group, we detected significantly lower skewness (t(84) = 2.500, $p = 0.014$; BF: 3.41), but similar c.o.v. in higher-ELC ASD toddlers (t(84) = 1.693, $p = 0.094$; BF: 0.83). Relative to the SIB group, we detected significantly lower skewness (t(78) = 2.580, $p = 0.012$; BF: 4.02), but similar c.o.v. in higher-VIQ ASD toddlers (t(78) = 1.754, $p = 0.083$; BF: 0.91). Relative to the SIB group, we detected significantly lower skewness (t(78) = 2.030, $p = 0.046$; BF: 1.41), but similar c.o.v. in higher-PIQ ASD toddlers (t(78) = 1.332, $p = 0.187$; BF: 0.53) (Figures 4C and 4D).

Relative to typically developing FA toddlers, we detected significantly lower skewness (t(75) = 2.188, $p = 0.032$; BF: 1.89) but similar c.o.v. (t(75) = 1.275, $p = 0.206$; BF: 0.51) in higher-DQ ASD toddlers. We detected similar skewness (t(81) = 1.907, $p = 0.060$; BF: 1.17) and c.o.v. (t(81) = 0.821, $p = 0.414$; BF: 0.34) in higher-ELC ASD toddlers. We detected similar skewness (t(75) = 1.9796, $p = 0.0514$; BF: 1.32) and similar c.o.v. (t(75) = 0.918, $p = 0.362$; BF: 0.37) in higher-VIQ ASD toddlers. We detected similar skewness (t(75) = 1.481, $p = 0.143$; BF: 0.65) and c.o.v. (t(75) = 0.452, $p = 0.652$; BF: 0.28) in higher-PIQ ASD toddlers (Figures 5A–5D).

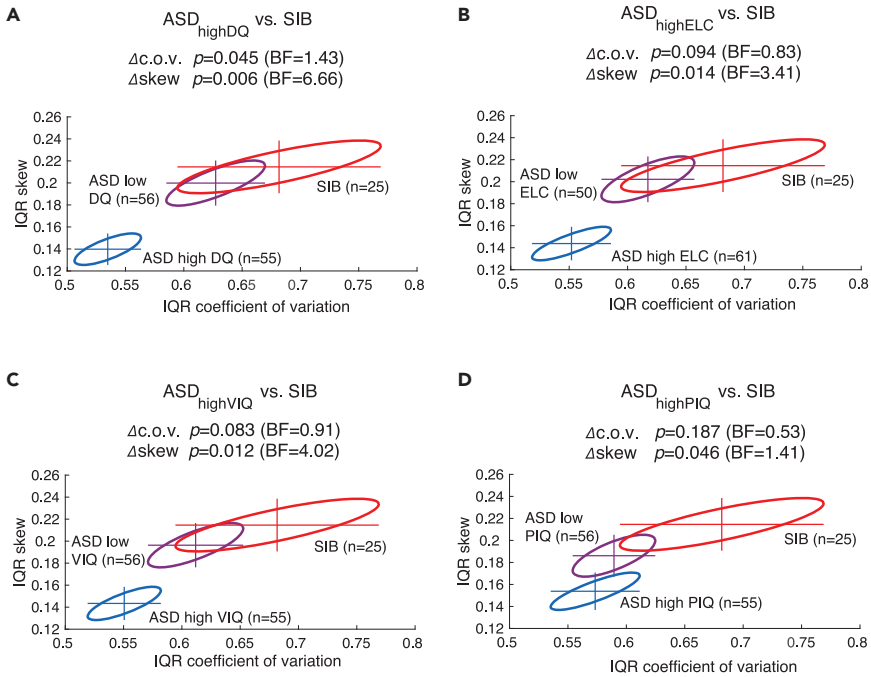

Figure 4. Sensorimotor features of infants who are biological siblings of an autistic child (SIB), and who are ascertained as neurotypical, are shown with toddlers with autism spectrum disorder (ASD) who have lower or higher cognitive abilities

SIB toddlers have average or above average IQ; their sensorimotor features are significantly different from the higher-IQ ASD group for DQ, ELC, VIQ, and PIQ. Plotted as in Figure 2. (Ellipses show standard error of the mean with lines showing cardinal standard errors.) Panel subgroupings based on (A) full-scale Developmental Quotient (DQ), (B) full-scale Early Learning Composite (ELC) standard score, (C) verbal IQ (VIQ), and (D) performance IQ (PIQ). Results (higher-IQ ASD vs. SIB) for DQ: skew, t(78) = 2.810, p = 0.006; BF: 6.66; c.o.v., t(78) = 2.036, p = 0.045; BF: 1.43; ELC: skew, t(84) = 2.500, p = 0.014; BF: 3.41; c.o.v., t(84) = 1.693, p = 0.094; BF: 0.83; VIQ: skew, t(78) = 2.580, p = 0.012; BF: 4.02; c.o.v., t(78) = 1.754, p = 0.083; BF: 0.91; PIQ: skew, t(78) = 2.030, p = 0.046; BF: 1.41; c.o.v., t(78) = 1.332, p = 0.187; BF: 0.53. *Note*: IQ, Intelligence Quotient; BF: Bayes Factor.

These findings demonstrate that the nature of early sensorimotor features during sleep in the higher-IQ ASD group is indistinguishable from the normative sensorimotor patterns of TD healthy control toddlers, while it is significantly different relative to that in the typically developing SIB group (and, to a lesser extent, relative to the FA group).

Significantly reduced motor skills in lower-IQ vs. higher IQ toddlers with ASD during wakefulness

Sensorimotor variability findings with lower-IQ vs. higher-IQ ASD toddlers are based on quantitatively acquired movements during natural sleep while children were scanned during fMRI studies. In the second set of analyses with an independent sample of infants (Sample #2), we sought to examine whether the general association of altered movement features with ELC in ASD would hold when movement data are based on observational instruments, and collected during wakefulness in an independent, very large sample of infants and toddlers who went on to receive ASD diagnoses in toddlerhood.

We find that in infancy, lower-ELC autistic children have significantly lower gross motor (GM) scores on MSEL relative to higher-ELC autistic children. These between-group differences hold at each of the age-bins tested (all p values <0.05). Specifically, motor skills were significantly lower for those with lower IQ at 6 months, t(230) = 3.7958, p = 1.8825e-04 (BF: 108.27), at 12 months, t(317) = 2.3605, p = 0.0189 (BF: 2.49), at 18 months, t(211) = 5.3537, p = 2.2421e-07 (BF: 5.5396e+04), at 24 months, t(383) = 5.1259, p = 4.7077e-07 (2.5597e+04), and at 30 months t(89) = 5.1338, p = 1.6550e-06 (BF: 8.7771e+03) (Figure 6).

These findings from the subgrouping analysis hold for the Spearman's correlation between ELC and GM scores. Higher ELC scores were associated with higher GM scores: at 6 months, r_s (230) = 0.3609, p = 1.5159e-08, at 12 months, r_s (317) = 0.1807, p = 0.0012, at 18 months, r_s (211) = 0.5287, p = 9.7195e-17, at 24 months, r_s (383) = 0.4001, p = 3.1337e-16, and at 30 months r_s (89) = 0.5934, p = 5.6803e-10 (Figure S9).

Findings were consistent when analyses were conducted separately for lower- vs. higher-IQ males and females with ASD, with findings reaching significance for males with lower vs. higher IQ at all age bins tested. Lower-IQ (vs. higher-IQ) males had significantly lower GM skills at 6, 12, 18, 24, and 30 months, and lower-IQ (vs. higher-IQ) females had significantly lower GM skills at 18 and 30 months. Specifically, findings indicate that GM skills assessed during wakefulness were lower with those males with lower IQ at 6 months, t(161) = 3.3667, p = 9.5145e-04, at 12 months t(228) = 2.1228, p = 0.0348, at 18 months, t(163) = 4.3136, p = 2.7748e-05, at 24 months t(285) = 5.6639, p = 3.6144e-08, and at 30 months t(78) = 4.6213, p = 1.4841e-05. Findings for females indicate that GM skills were lower with those with lower IQ at 6 months,

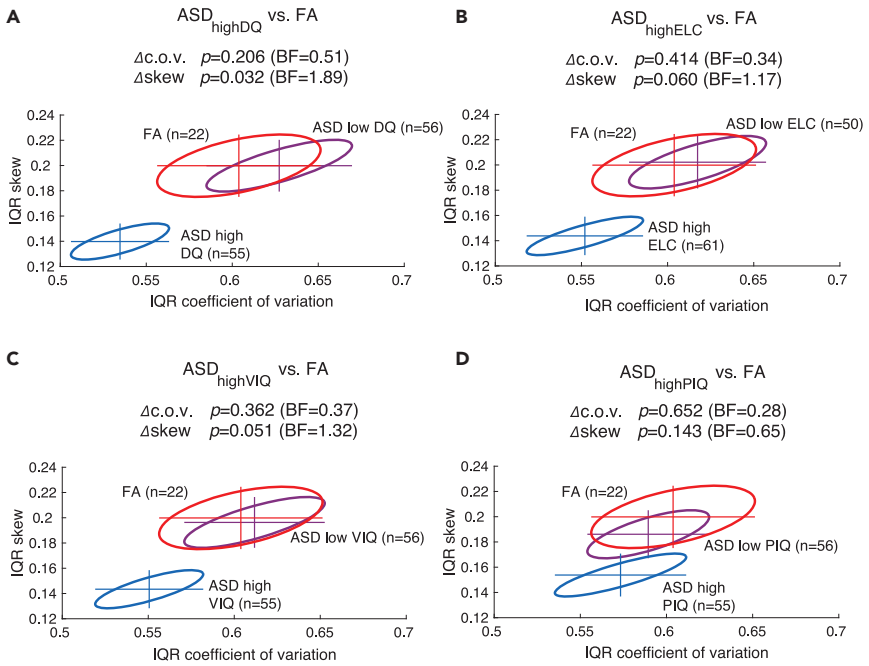

Figure 5. Sensorimotor features of infants who failed a pediatrician' screening (FA) at 12 months, and who are ascertained as neurotypical, are shown with toddlers with autism spectrum disorder (ASD) who have lower or higher cognitive abilities

FA toddlers have average or above average IQ; their sensorimotor features are significantly different from the higher-IQ ASD group for DQ. Plotted as in Figure 2. (Ellipses show standard error of the mean with lines showing cardinal standard errors.) Panel subgroupings based on (A) full-scale Developmental Quotient (DQ), (B) full-scale Early Learning Composite (ELC) standard score, (C) verbal IQ (VIQ), and (D) based on performance IQ (PIQ). Results (higher-IQ ASD vs. FA) for DQ: skew, $t(75) = 2.188$, $p = 0.032$; BF: 1.89; c.o.v., $t(75) = 1.275$, $p = 0.206$; BF: 0.51; ELC: skew, $t(81) = 1.907$, $p = 0.060$; BF: 1.17; c.o.v., $t(81) = 0.821$, $p = 0.414$; BF: 0.34; VIQ: skew, $t(75) = 1.9796$, $p = 0.0514$; BF: 1.32; c.o.v., $t(75) = 0.918$, $p = 0.362$; BF: 0.37; PIQ: skew, $t(75) = 1.481$, $p = 0.143$; BF: 0.65; c.o.v., $t(75) = 0.452$, $p = 0.652$; BF: 0.28. *Note*: IQ, Intelligence Quotient; BF: Bayes Factor.

$t(67) = 1.8084$, $p = 0.0750$ (n.s.), at 12 months $t(87) = 0.7934$, $p = 0.4297$ (n.s), at 18 months, $t(46) = 3.1873$, $p = 0.0026$, at 24 months $t(96) = 1.0245$, $p = 0.3082$ (n.s.), and at 30 months $t(9) = 3.5396$, $p = 0.0063$.

Overall, both datasets show that altered sensorimotor features during sleep (Sample #1) and during wakefulness (Sample #2) are significantly associated with lower cognitive abilities in toddlers with early childhood autism.

DISCUSSION

We found important evidence that sensorimotor features in toddlers who went on to receive ASD diagnoses in early childhood are correlated with their cognitive abilities. These motor system characteristics are neurobiological precursors of how our brains map motor and cognitive experience for successful learning, and we found that alterations in these precursors are significantly associated with the integrity of cognitive abilities. Overall, relative to higher-IQ ASD toddlers, those with lower-IQ have altered skewness and coefficient of variance parameters with data acquired during natural sleep. These findings are consistent for males and females, when excluding infants at high familial likelihood for autism, as well as across different scan conditions, establishing a strong, context-independent link between altered motor development and cognitive impairment in autism. We further find that higher cognitive abilities in autistic toddlers cf. resilience to atypical movement (or vice versa), as sensorimotor features in higher-IQ toddlers are indistinguishable from those of neurotypical, typically developing healthy control toddlers who have average IQ. Importantly, we confirm the association between these altered motor features during sleep and lower IQ in autism in an extremely large, independent sample of autistic children who had their motor skills assessed in infancy and toddlerhood during wakefulness. Autistic children with lower IQ have significantly lower GM skills at every age tested: at 6, 12, 18, 24, and 30 months.

The discovery of this link in children with ASD means that motor and cognitive abilities *are not independent* in children who are diagnosed with autism early in life, during preschool. Notably, in our main sample, we detected a significant association between lower VIQ and higher asymmetry (skewness), with "substantial" Bayesian evidence for boys (Bayes Factor 6). To our knowledge, our result is the first to quantitatively establish a link between altered sensorimotor features during sleep and impaired verbal skills in toddlers from the population at large who were later diagnosed with ASD. Greater variability and skewness were also associated with lower developmental quotient (DQ), with "strong" Bayesian evidence in autistic boys on the skewness parameter (Bayes Factor 34). These findings are congruent with patterns seen in studies with adults, such that "noise has direct behavioral consequences"[34] and the earliest study to date in 1–2 month-old infants at higher familial likelihood (HL) for autism, such that relative to LL infants, atypically higher movement variability in infancy is associated with worse cognitive abilities in the future.[19]

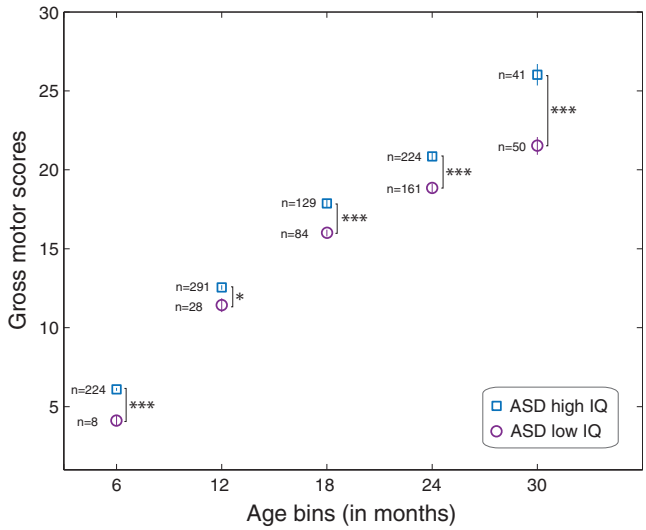

Figure 6. Lower gross motor (GM) scores during wakefulness in an independent sample of infants and toddlers with autism spectrum disorder (ASD) outcomes who have lower full-scale IQ (ELC), relative to autistic children with higher full-scale IQ

GM skills are ascertained during wakefulness. Lower GM scores indicate lower motor skills. Significantly lower motor functioning is detected in children with ASD with lower IQ, within each of the age bins tested at 6, 12, 18, 24, and 30 months (Data shown are means with error bars representing +/− s.e.m. [+/− standard error of the mean]). *: $p < 0.05$; ***: $p < 0.001$. Results (higher-IQ vs. lower-IQ ASD toddlers) at 6 months, t(230) = 3.7958, p = 1.8825e-04 (BF: 108.27); at 12 months, t(317) = 2.3605, p = 0.0189 (BF: 2.49); at 18 months, t(211) = 5.3537, p = 2.2421e-07 (BF: 5.5396e+04); at 24 months, t(383) = 5.1259, p = 4.7077e-07 (2.5597e+04); and at 30 months, t(89) = 5.1338, p = 1.6550e-06 (BF: 8.7771e+03). *Note*: IQ, Intelligence Quotient; ELC, Early Learning Composite standard score. BF: Bayes Factor.

In particular, previous evidence strongly suggests that alterations in motor features, such as heightened motor variability during wakefulness broadly impedes learning.[34] Indeed, increased noise levels impair learning because "variability from noise limits the ability to learn from reinforcement feedback."[9] The consequences of heightened motor variability include reduced movement precision[34] subsuming eye gaze, body, and head movements. Earlier research also points to the fundamental role of sensorimotor circuitry during vocal or first language learning, a process guided by a social tutor in juvenile birds (zebra finches)[35] and human infants.[21] Interestingly, sensorimotor regions in songbirds modulate circuit changes,[36] which normally support learning during early development,[37] and impairment of sensorimotor circuitry in songbirds is detrimental to song production.[38]

Lower-IQ ASD toddlers have altered sensorimotor features: Implications for early learning

Altered sensorimotor features spanning a sensitive or critical period in development may suggest a nascent anomaly with reinforcement learning (RL) or error-based learning. Specifically, sensorimotor alterations during ongoing maturation may interfere with RL and error-based mechanisms in spontaneous, natural settings, including during evolutionarily important social interactions that become rewarding with time in normal development. Within the RL framework, "exploratory actions are tried out and each action's outcome is evaluated; learning aims to maximize the value of future action choices."[39] Indeed, a fundamental component of motor control is the brain's coordination of movement during natural behavior.[2,3] Moreover, studies using animal models indicate that in early development, motor cortex establishes "a sensory framework" that *later scaffolds nascent motor control*.[40] We suggest that such sensory framework within the motor cortex may be less well developed in toddlers with ASD who have impaired early cognition.

Herein, we posit that altered sensorimotor features during sleep detected in Sample #1, and impaired GM skills during wakefulness detected in Sample #2, limit the ability of RL to act[8,9] during critical, sensitive period in development and therefore contributes to the poor-motor ASD subtype characterized by poorer cognitive abilities. As we argue, it is highly unlikely that the consequences of such altered motor features are restricted to sleep-related activity; rather, these likely portend broader problems with early motor processing and early learning in early childhood autism.

The combination of altered motor features and lower IQ in ASD toddlers may act as a "double dose" of impairments that likely interact and both may interfere with early learning. Lower cognitive abilities may limit knowledge acquisition in a domain-specific manner. For example, the infant's attention may not be directed to relevant examples within the social core domain of thinking.[41] If so, he or she may have difficulty building a representation of action outcomes and have greater uncertainty or difficulty associating them with putative reward values.[39] Thus, in early infancy, lower IQ may impact early infant social understanding and reduce ability to infer causality and engage in nascent causal reasoning about other minds. This interpretation is consistent with the notion that domain-general mechanisms, such as general cognitive ability or memory can develop and contribute differently to content of different domains.[42] For example, lower IQ may particularly interfere or delay social concept acquisition and ability to acquire information about "mental states" of other people.[16] The course of conceptual development may be impacted in these lower-IQ ASD toddlers.

Although our study is by definition correlative, we speculate that impaired early IQ coupled with altered motor features may reduce opportunities for initiation of social or non-social communicative interactions. When eager to communicate about something interesting that they see, by 12 months neurotypical infants not only point to a visual object that interests them, but also they use gaze to check if the caregiver is looking at what they are showing.[43] They look around to attract the attention of the mother or caregiver to the same object (see in the study by Ricks et al.[44]), turning their heads or bodies in the process. In our study, autistic infants with altered motor features and lower IQ may point imprecisely to what they would like to show, miss caregiver cues of gaze directed to them, or delay their timing to quickly check if the caregiver is looking. It is important to highlight additional features that distinguish lower- vs. higher-IQ toddlers in the main sample, as these may further interact with altered motor features as well as with lower cognitive abilities. Specifically, relative to higher-IQ ASD toddlers, lower-IQ toddlers have significantly greater autism manifestations on the ADOS (e.g., Total and SA CSS score) and significantly lower adaptive functioning on the VABS-II (e.g., ABC composite score).

Do higher-IQ ASD toddlers have normative head movement patterns?

A key follow-up question in our work concerns the nature of movements in the *higher* IQ ASD subgroup relative to children with neurotypical outcomes. Are head movements of this higher IQ ASD group "typical" or "atypical"?

We find that the higher-IQ ASD group's motor features are indistinguishable from those in the TD healthy control group (characterized by average or slightly above-average cognitive abilities, no genetic risk or likelihood for autism, and no previous or current developmental concerns), thereby revealing that higher-IQ ASD toddlers have typical or "normative" motor features. With this finding, our current study adds to the body of research that characterizes features of children ascertained with ASD and good intellectual abilities. Previous research has shown that those infants with ASD diagnoses in early childhood who have had higher cognitive abilities are also characterized by higher adaptive functioning scores (on the Vineland), compared to adaptive functioning in neurotypical children with lower cognitive abilities.[15] For toddlers in the current study, higher cognitive abilities of autistic toddlers may confer resilience toward developing more normative sensorimotor features, or conversely, their normative sensorimotor features may confer resilience toward improved cognitive abilities.

However, the sensorimotor features of the higher-IQ ASD vis-à-vis "typical" development groups should be considered within the context of latent biological risk or potential previous concerns—even when comparing among children with neurotypical outcomes and average IQ. In this cohort of toddlers, we found that sensorimotor features, IQ, and developmental outcomes interact in a complex manner. Intriguingly, higher IQ alone does not necessarily associate with improved sensorimotor features in neurotypical toddlers, as shown by analyses with SIB and FA groups. In particular, motor features of the SIB group are significantly worse relative to the higher-IQ ASD group, suggesting that the latent genetic risk may contribute to sensorimotor differences between the groups.

Taken together, the association between sensorimotor functioning, cognitive abilities, and developmental outcomes appears to be complicated by risk factors: genetic in the case of the neurotypical SIB group and non-genetic in the case of the neurotypical FA group. Both of these groups have average IQ, but their motor features are worse relative to the higher-IQ ASD group. Therefore, it is possible to observe a combination of higher-IQ, normative developmental outcomes, and yet altered sensorimotor features. Remarkably, however, across the available comparison groups in this study, we did not observe a combination of both low IQ and normative sensorimotor features.

New questions arising: *trans*-Diagnostic window on intellectual impairment

While our results robustly characterize toddlers with ASD outcomes, we allow for the possibility that these findings may not be necessarily specific to autism but may reflect atypical development in general. If so, it might well be that the study has opened a new window on intellectual impairment—trans-diagnostically. First, we emphasize that the sensorimotor features of higher-IQ ASD toddlers are significantly different from those of lower-IQ ASD toddlers. As such, this finding may indicate more broadly that a specific combination of lower cognitive abilities and altered sensorimotor features may characterize a set of toddlers with atypical developmental outcomes in early childhood. Second, we found that the sensorimotor features of higher-IQ ASD toddlers are also significantly different from those of the neurotypical SIB group. In this case, the altered sensorimotor features of the SIB group can serve as a "red flag", an indicator of concern, for these healthy children at familial likelihood for autism, as they may nevertheless develop ASD or other neurodevelopmental, neuropsychiatric, or neurophysiological disorders in the future—in later childhood or adolescence. These children's higher cognitive abilities may "rescue" them such that at present, these children are not ascertained with atypical development. Nevertheless, their altered sensorimotor features may augur potential future neuropsychiatric challenges, such as anxiety, depression, and sleep disturbances.

To answer the question of whether the findings are specific to autism *per se*, it would be necessary to include a subgroup of children with low IQ but without autism (e.g., such a group may be characterized by a neurogenetic condition associated with intellectual disability). Such a group was important to have in the early days of autism research[45] but at present it is challenging to assemble in part due to current research and diagnostic practice (e.g., there are only 3 such children within the larger cohort of participants, who have cognitive abilities below 70 on the ELC and are neither ascertained with any developmental disorder nor are deemed typically developing). For example, we may hypothesize that toddlers with low cognitive abilities and an underlying neurogenetic condition (e.g., Fragile-X syndrome) may also have altered sensorimotor features (i.e., due to the genetic overlap between motor and cognitive genes;[46]), although they may not necessarily be ascertained with ASD. If so, there are important reasons to characterize sensorimotor features in this population as well, as alterations could augur symptom severity on variables related to quality of life and adaptive functioning. This is a new question arising from the current study and it remains a goal for our future research in early childhood autism.

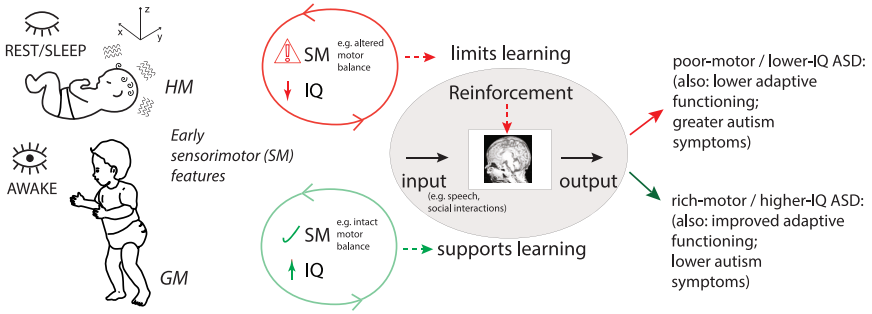

Figure 7. Consequences of poor vs. rich early sensorimotor features in preschool children with autism spectrum disorder (ASD)
The brain's motor control circuitry is vulnerable to impaired early sensorimotor features, which limits the ability of reinforcement (or error based) learning to act, and is associated with lower cognitive abilities in toddlers with ASD. HM, head movements; GM, gross motor.

Infant-specific conceptual model

We introduce an infant-specific conceptual model of how early differences in sensorimotor features might have a causal impact on future development (Figure 7). The upper-left portion of Figure 7 shows that early poor sensorimotor features (i.e., increased motor variability during sleep, Sample #1, as well as lower GM skills during wakefulness, Sample #2) are associated with lower IQ. The middle panel shows how impediments in early information processing may lead to atypical learning and development, including suboptimal neural processing under cognitively- and sensorimotor-demanding conditions, in some children who go on to receive ASD diagnoses. These features may lead to "poor-motor/lower-IQ ASD subtype" shown in the upper-right portion of Figure 7. We emphasize that the specific combination of both altered sensorimotor features and lower cognitive abilities characterizes poor-motor/lower-IQ ASD subtype.

Conversely, the lower-left portion of Figure 7 shows that when the relatively richer early sensorimotor features are coupled with higher IQ as well as with improved additional behaviors in ASD, it augurs richer and more efficient neural processing supportive of learning (middle panel). Rich-motor early functioning "rescues" and scaffolds more normative cognitive functioning and coordination of social attention in children diagnosed with ASD in early childhood (or, conversely, more normative early cognition interacts more efficiently with more normative motor functioning), leading to the "rich-motor/higher-IQ ASD subtype" shown in the lower-right portion of Figure 7.

Limitations of the study

One key limitation of our study is that there are no interventions and as such our results can only be correlative. However, using prior work in the field we suggest that the sensorimotor features may be partly causal in affecting the cognitive features. To confirm this hypothesis will require future studies. In addition, it may be possible that the higher-ELC and lower-ELC groups differ on some other characteristics that could impact head movement features. While information about trait-level activity/hyperactivity (ADHD-like symptoms) is unavailable for these subjects, it would be important to consider the impact of these comorbid features on sensorimotor features in future research. However, we note this knowledge would be unlikely to change the outcomes in this study due to the extremely large number of participants across Samples #1 and #2. Moreover, for Sample #1, we lack information on depth or stage of sleep during scanning (such as quiet or active sleep), and movements differ across stages.[47] While this caveat is not unique to our work and is common to most fMRI scans at the present time, it would be important to measure sleep states during MRI scans and take these variables into account in future research.

Importantly, our current findings establish the first empirical link between sensorimotor features and cognition (during sleep, as well as during wakefulness) in children before they are diagnosed with ASD. As such, we provide an important first step toward neurobiologically grounded brain imaging studies of precursors of autism in infants, because we show that altered sensorimotor movements are linked meaningfully to a variety of functional outcomes in these toddlers, across the different cognitive and other contexts.

One significant implication of our findings is that some children with ASD who have the "rich-motor/higher-IQ" subtype in toddlerhood may be better able to cope with social demands, as these children have higher cognitive abilities (as well as better adaptive functioning and lower autism manifestations). Their sensorimotor features are indistinguishable from typically developing healthy control toddlers. In this regard, our findings help inform an important debate in the field, on new potential subtypes or prototypes of ASD[17,48] (including subtypes on the spectrum, distinguished by severity such as "profound IQ" [IQ < 50] subtype[49]). As such, our findings of altered sensorimotor features in children with lower cognitive abilities have clinical implications for development of more precise treatments and supports for infants and their families, since requirements for supports could differ by subtype.[15] For example, sensorimotor experience may not necessarily be an important target for intervention for higher-IQ autistic children, as they have relatively typical motor features and IQ. Instead the focus could be on leveraging their strengths to recognize and mitigate downstream mental health consequences of compensation or camouflaging, which is thought to occur predominantly in autistic individuals with higher IQ.[50] In contrast, interventions for lower-IQ autistic children may differ in their focus, improving both sensorimotor *and* cognitive skills, but not either one alone, in order to increase both precision and the likelihood of generalizability of the improvements to other contexts and domains.

In summary, our findings are the first to show that toddlers with ASD who have lower IQ have a different sensorimotor phenotype relative to those who have higher IQ. The brain's motor control circuitry may be vulnerable to impaired early sensorimotor features and this

"poor-motor" state is associated with lower cognitive abilities in toddlers who receive an ASD diagnosis. Our findings are potentially relevant for development of more precise interventions tailored to subtypes of early childhood autism.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
  - Experimental design
  - Main sample: Sample #1
  - Independent sample: Sample #2
- METHOD DETAILS
  - Procedures: Main sample (Sample #1)
  - MRI acquisition parameters (Sample #1)
  - Assessing infant intelligence: Samples #1 and #2
- QUANTIFICATION AND STATISTICAL ANALYSIS
  - Statistical analyses: Main sample (Sample #1)
  - Subgroupings by cognitive abilities: Sample #1
  - Statistical analyses: Independent sample (Sample #2)
  - Subgroupings by cognitive abilities: Sample #2

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110685.

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AUTHOR CONTRIBUTIONS

Designed study: K.D. and D.M.W.; analyzed data: K.D. and D.M.W.; wrote paper: K.D. and D.M.W.; obtained funding: K.D. and D.M.W.

DECLARATION OF INTERESTS

D.M.W is a consultant to CTRL-Labs Inc., in the Reality Labs Division of Meta. This entity did not support or influence this work.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Data (MRI, behavioral, clinical)	NDA repository	https://doi.org/10.15154/qfej-cf04
Software and algorithms		
MATLAB	The MathWorks, Inc., Natick, MA	http://www.mathworks.com
Statistical Parametric Mapping (SPM)	Friston[31–33]	http://www.fil.ion.ucl.ac.uk/spm/software
Bayes Factor	Kass[51]	https://github.com/klabhub/bayesFactor

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Kristina Denisova (kristina.denisova@qc.cuny.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- De-identified human/patient data used in the preparation of this manuscript are within the public depository maintained by the NDA (NIMH Data Archive, formerly known as NDAR). NDAR is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in autism, and data are available to qualified researchers via a data-sharing agreement. Dataset identifier: https://doi.org/10.15154/qfej-cf04.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Experimental design

This study uses fMRI, behavioral, and clinical data from the NIH-supported National Database for Autism Research (NDAR). NDAR is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in autism. The focus of the current work is to examine cognitive and sensorimotor features in infants and toddlers before they receive ASD diagnoses in early childhood. There are two samples with which we study movements in autism: (*i*) the main sample with head movements characterized during sleep fMRIs (Sample #1), and (*ii*) an independent sample with gross motor skills characterized using observational instruments during wakefulness (Sample #2).

Our study is designed to parse heterogeneity related to cognitive and sensorimotor features within toddlers with ASD. The primary analyses are conducted all within the ASD group; there are several reasons for this. Recent prospective work has established that cognitive abilities in early infancy and toddlerhood are significantly lower in children later diagnosed with autism relative to those typically developing.[15] In addition, sensorimotor deficits, such as delays in age at walking alone in children with autism is a consistent finding (e.g.,[52]), related to a higher likelihood for disruptive *de novo* mutations in ASD-associated genes.[52] Indeed, about 28% of autistic children from autism simplex families (defined as one child with autism) are estimated to harbor *de novo* mutations,[53] and diminished motor skills and lower non-verbal IQ are distinctly related to a higher vulnerability score on a likely gene disrupting (LGD) or missense target.[54] These findings suggest an overlap in the genetic basis of diminished IQ and motor skills in ASD, in addition to the genetic overlap between intellectual disability and ASD (cf.[50]). An autistic child with phenotypic impairments in both motor and cognitive abilities likely has different neurobiological substrates that underwrite these impairments, relative to children with typically developmental outcomes. Comparing to typically developing toddlers is generally problematic because the distribution of IQ scores of each group is substantially different from the ASD groups. First, splitting a typically developing group based on median or mean IQ would not be a fair comparison. Second, matching the IQ scores is hard as most ASD toddlers have scores 2 SD below typically developing.[15] For example, in the MRI dataset detailed below (main Sample #1) there are no typically developing children with an IQ below 70 (the cut-off on the ELC we used to split the ASD group). As such, comparisons within an ASD

population are uniquely suited for understanding heterogeneity within autism, particularly heterogeneity related to cognitive abilities. For the main sample, we compute comparisons between the higher-IQ ASD subgroup relative to several neurotypically developing groups.

All data are de-identified in compliance with U.S. Health Insurance Portability and Accountability Act (HIPAA) guidelines. Research protocols (including neuroimaging, behavioral, and clinical assessments) were reviewed and approved by the original investigators' Institutional Review Board, and signed written informed parental consent was obtained by original study investigators in accordance with U.S. 45 CFR 46 and Declaration of Helsinki for participation. Analyses of these de-identified data were reviewed and approved by the Institutional Review Boards of City University of New York (CUNY Human Research Protection Program, HRPP IRB 2021–2057) and Columbia University (CU IRB-AAAU2087). They made a formal determination that this work constitutes 'not-human subjects research' and an exemption from further consent was granted.

Main sample: Sample #1

Participants were 202 toddlers who received ASD diagnoses or were ascertained as typically developing, at 3–4 years. Infants met inclusion criteria during recruitment at the Autism Center of Excellence (ACE) at UCSD (University of California, San Diego). The dataset identifier (along with the Submitter) is NDARCOL0000009 (Collection 9, Karen Pierce). A key feature of this ACE is recruitment of infants from the population at large (i.e., toddlers are not at a biologically heightened risk or likelihood for autism due to an older biological sibling with ASD). At ACE UCSD, toddlers were recruited into the cohort using a general population screening method or community referrals. Specifically, infants were recruited via ACE UCSD's website, via referrals from the community, as well as by participating pediatricians (e.g.,[55]). Recruitment based on pediatricians' referral involved completion of a well-baby check-up (1-Year Well-Baby Check Up Approach[56]/Get S.E.T. Early Model[57]) around 12 months of age at participating pediatricians' offices, which identified infants at potential risk for atypical development.

For toddlers with multiple clinical assessments, autism determination is based on the latest date of the assessment. Toddlers were administered the Autism Diagnostic Observation Schedule, ADOS (Generic, ADOS-G[58] by research-reliable staff at ACE UCSD. Diagnoses made using the DSM-IV criteria (Autism, Autism Spectrum Disorder, Pervasive Developmental Delay – Not Otherwise Specified, PDD-NOS) were converted to DSM-5 diagnosis of Autism Spectrum Disorder, ASD.[59] The diagnosis of ASD was made on the basis of the ADOS administration for all participants, available history and parental interviews (including (ADI-R[60]), and expert clinical opinion. Revised ADOS algorithms were used (Gotham et al., 2007; 2008[61,62]). Calibrated Severity Scores (CSS) (for Social Affect, SA, Restricted and Repetitive Behaviors, RRB, and Total) on the ADOS were computed for all children for whom item-level scores and language level (A1 item) information was available, according to Esler et al.[63] for the Toddler Module and for additional Modules (covering 1, 2, and 3) according to Gotham et al. and Hus et al.[64,65]

For infants with multiple assessments on the Mullen, the earliest date of assessment was used so as to be as close as possible to the time of the first scan. Within this set of infants, we also report adaptive functioning scores (Vineland Adaptive Behavior Scales-II; VABS-II[66]) for high vs. low IQ (ELC) subgroups.

Inclusion criteria for participants in this study were availability of ASD diagnosis (or ascertainment of typical development) in toddlerhood, by around 36–48 months of age, infants who have undergone several functional Magnetic Resonance Imaging (fMRI) scans during natural sleep, and for whom early learning measures on the Mullen Scales of Early Learning (MSEL)[67] were available. Excluded were infants with missing fMRI data (N=499), as well as those missing resting-state, speech, or social orienting fMRI scans (N=7), missing Mullen data (N=16); missing ASD or neurotypical outcomes (N=49), or missing both Mullen data and outcomes (N=2).

The ASD group included 111 unique toddler participants (mean age ± sd: 30.19 ± 9.15) with resting-state, speech, or social orienting fMRI scans and behavioral and clinical assessments, after excluding one participant with unusable fMRI data. Overall for this sample the Male to Female ratio (M/F) was 88M/23F; the sex of participants was based on parental report. This ratio (3.8, with more ASD males than ASD females) is consistent with greater prevalence of boys than girls in the ASD population according to the US Centers for Disease Control (CDC). This ratio is very close to the ratio reported in the latest prevalence report by the CDC: 3.8 for 8-year old children with ASD[68] and 3.1 for 4-year old children with ASD.[69] Power analysis was not performed because these data were already collected and in existence, and our sample of toddlers with ASD is larger that most autism studies (e.g.[70]). Power analysis is normally performed before data collection to estimate the number of subjects needed to be enrolled to achieve significant between-group differences; analysis after data collection is controversial[71,72] (cf.[73]; p. e297).

Among neurotypical toddlers, a group of typically developing (TD) healthy controls (N=44; 22M/22F; mean age ± sd: 28.62 ± 11.41) subsumed children who were recruited to the study as part of the healthy control cohort and were ascertained as typically developing; none had known risks for autism or previous delays or concerns. In addition, there was (*i*) a high-risk siblings (SIB) group (N=25; 16M/9F; mean age ± sd: 20.50 ± 7.48) subsuming children who were ascertained as developing typically and had no previous delays or concerns, but who were biological siblings of a child with ASD, and (*ii*) a failed developmental screener (FA) group (N=22; 14M/8F; mean age ± sd: 22.83 ± 9.58), which subsumed children who were also ascertained as developing typically but who all failed the developmental screener around 12 months of age.

Thus, a total of 202 unique toddlers were included in this study: those who were ascertained to have ASD (N=111) and those for whom ASD was ruled out and who were ascertained as neurotypical children, broken down into TD healthy controls (N=44), SIB (N=25), and FA (N=22).

Demographic characteristics of the ASD sample (based on parental report) are as follows: White, N=57; more than one race, N=10; Black or African American, N=6; Asian, N=5 (Race was not reported for N=33 participants). Eight participants were Hispanic or Latino and 17 were non-Hispanic or Latino (Ethnicity was not reported for N=86 participants). All N=111 participants had available ADOS CSS scores (mean ± sd): SA CSS: 6.30 ± 1.72; SA RRB: 7.11 ± 1.54; Total CSS: 6.46 ± 1.81. The scores on the MSEL for the overall sample (N=111) were (mean ± sd): ELC: 74.41 ± 17.66; VIQ: 64.84 ± 23.52; PIQ: 88.54 ± 18.38; DQ: 76.69 ± 19.29.

Demographic characteristics of the TD healthy control sample (based on parental report) are as follows: White, N=27; more than one race, N=1; Black or African American, N=3; Asian, N=1; Hawaiian or Pacific Islander, N=2 (Race was not reported for N=10 participants). One participant was Hispanic or Latino and 5 were non-Hispanic or Latino (Ethnicity was not reported for N=38 participants). All N=44 participants had available ADOS CSS scores (mean ± sd): SA CSS: 1.31 ± 0.51; SA RRB: 1.59 ± 1.51; Total CSS: 1.09 ± 0.29. The scores on the MSEL for the overall sample (N=44) were (mean ± sd): ELC: 112.00 ± 13.49; VIQ: 110.50 ± 14.98; PIQ: 117.39 ± 12.21; DQ: 113.94 ± 11.25.

Demographic characteristics of the SIB sample (based on parental report) are as follows: White, N=16; more than one race, N=2; (Race was not reported for N=7 participants). None of the participants were Hispanic or Latino and 3 were non-Hispanic or Latino (Ethnicity was not reported for N=22 participants). In the SIB subgroup, N=24 out of 25 participants had available ADOS CSS scores (mean ± sd): SA CSS: 1.79 ± 1.79; SA RRB: 2.08 ± 2.41; Total CSS: 1.62 ± 1.63. The scores on the MSEL for the overall sample (N=25) were (mean ± sd): ELC: 105.68 ± 17.97; VIQ: 103.65 ± 19.53; PIQ: 115.81 ± 17.80; DQ: 109.73 ± 17.37.

Demographic characteristics of the FA sample (based on parental report) are as follows: White, N=17; more than one race, N=1; Asian, N=1 (Race was not reported for N=3 participants). None of the participants were Hispanic or Latino and 1 was non-Hispanic or Latino (Ethnicity was not reported for N=21 participants). All N=22 participants had available ADOS CSS scores (mean ± sd): SA CSS: 1.5 ± 0.67; SA RRB: 2.41 ± 2.15; Total CSS: 1.31 ± 0.64. The scores on the MSEL for the overall sample (N=22) were (mean ± sd): ELC: 98.77 ± 9.99; VIQ: 97.36 ± 11.76; PIQ: 111.40 ± 12.06; DQ: 104.38 ± 10.44.

Independent sample: Sample #2

Participants were infants and toddlers who received ASD diagnoses at 3-4 years, and who had available, valid gross motor (GM) assessments on the MSEL. These participants are from a larger sample of children from birth to 68 months with ASD outcomes, which we characterized previously.[15] Briefly, infants met inclusion criteria during recruitment across 62 study-sites from 18 states in the US[15] and were assessed prospectively and some longitudinally on the MSEL, with ASD ascertained in early childhood.[15] (Note: infants in this sample do not overlap with those from the main sample #1, as no GM data were available for Collection 9 for infants with fMRI scans.).

GM is a separate scale of MSEL, administered during wakefulness up to around 33 months.[67] Similar to cognitive abilities, GM skills are tested using age-appropriate probes of graded difficulty.[67] Examples of increasing difficulty with age include a child being placed in a supportive position on the parent's lap and infant's ability to hold his or her head steady is observed, child being placed in a standing position and encouraged to walk 4-5 steps independently, without support, child observed to walk up stairs with help using non-alternating steps, child assessed for ability to jump down from bench, and child assessed for ability to walk on a line using arms to balance.

After applying inclusion criteria for valid age at GM administration, there were N=1,046 infants ages 3 to 33 months with available, valid GM AE scores on the MSEL and full-scale ELC (IQ) estimates, with N=676 infants contributing two and more assessment time points. AE-based GM scores were used in the current analysis. The Male to Female ratio (M/F) was 806M/240F (based on parental report). At 3.3, this ratio (with more ASD males than ASD females) is consistent with the ratios reported in the latest prevalence estimates according to the CDC: 3.8 for 8-year old children with ASD[68] and 3.1 for 4-year old children with ASD.[69] Available demographic characteristics of the sample (based on parental report) are as follows: White, N=12; more than 1 race, N=2; Black or African American, N=1; Asian, N=2. Two participants were Hispanic or Latino and 15 were non-Hispanic or Latino (Race or ethnicity was not reported for N=1029 participants).

Because of the age-related differences in motor probes, analyses were conducted for pre-specified age-bins, at 6, 12, 18, 24, and 30 months (+/- 1 month).

Ascertainment of ASD diagnoses is detailed in Denisova & Lin[15]; for children with multiple assessments, the latest date of the assessment was used. The average age at ADOS assessment for children with ASD was around 3.5 years (on average, about 43 months). Briefly, ascertainment was based on administration of the ADOS (either the Generic, ADOS-G[58] or ADOS-2[74]) for all participants, available history and parental interviews, and expert clinical opinion (ADI-R[60] parent interviews were also available for about 85% of subjects who had the ADOS as well as the clinical diagnosis). Revised ADOS algorithms[61,62] were used. Diagnoses made using DSM-IV criteria were converted to DSM-5 diagnosis of Autism Spectrum Disorder, ASD.[59] Calibrated Severity Scores (CSS) are computed for all children with available item-level scores and language level (A1 item) information, for Modules 1, 2 and 3 according to Gotham et al. and Hus et al.[64,65] and according to Esler et al.[63] for the Toddler module. N=1,025 children had available ADOS CSS scores (mean ± sd): SA CSS: 6.46 ± 2.46; SA RRB: 6.58 ± 2.58; Total CSS: 6.45 ± 1.99.

Demographic characteristics of both samples are provided in Table S1.

METHOD DETAILS

Procedures: Main sample (Sample #1)

In this cohort, infants underwent an fMRI during which speech was presented, an fMRI during which social sounds were presented, and a resting-state fMRI (silence; no sound stimuli were presented during the scan). Block design was used for both speech and social orienting scans. The speech language condition consisted of three blocks with speech stimuli (complex forward speech, simple forward speech, and backward speech) which were interleaved with rest blocks (no sounds). Each stimulus and rest block lasted 20 seconds; the initial rest interval at the onset of scan lasted 17 seconds and the rest interval at the end of the scan lasted 26 seconds. The social orienting condition consisted of three blocks of sound stimuli: social orienting sounds (alerting the child using a child-friendly and engaging tone of voice, e.g. "Over here, Clara, over here!"), language sounds (e.g. simple 2-3 word phrases) and non-speech environmental noise sounds (e.g. a ringing bell). Sound blocks were interleaved with rest blocks (no sounds). Duration of each stimulus block was 38 seconds. Each rest block lasted

6 seconds, except for three blocks that lasted 32 seconds; the initial rest interval at the onset of scan lasted 37 seconds and the rest interval at the end of the scan lasted 14 seconds.

A total of 405 datasets (194 for speech, 142 for social orienting, and 69 for resting-state scans) were available for these unique participants. Multiple runs of the same condition were combined where children had more than one MRI run. All runs from all conditions were combined for the main analyses (supplementary analyses also present a breakdown of findings for each condition). A total of 219 datasets (109 for speech, 77 for social orienting, and 33 for resting-state scans) were available for ASD. A total of 82 datasets (41 for speech, 27 for social orienting, and 14 for resting-state scans) were available for TD. A total of 57 datasets (25 for speech, 21 for social orienting, and 11 for resting-state scans) were available for SIB. A total of 47 datasets (19 for speech,17 for social orienting, and 11 for resting-state scans) were available for FA.

MRI acquisition parameters (Sample #1)

Functional Magnetic Resonance Imaging (fMRI) Blood Oxygenation Level-Dependent (BOLD) data were acquired using a T2*-weighted echo planar imaging (EPI) sequence at 1.5 Tesla MR scanner. The acquisition parameters [Time of Repetition/Echo Time, TR/TE: 2500/30 ms, flip angle=90°, FOV=256 mm, in-plane resolution=4 x 4 mm, 31 axial 4 mm slices] were the same for all three scans; scan duration was 6 min 24 s (154 volumes) for the rs-fMRI and speech scans, and 11 min 15 s (270 volumes) for the social orienting scan. (Note: the sampling rate for all scan conditions is the same at TR=2500 ms, or .4 Hz.).

MRI data were pre-processed using Statistical Parametric Mapping (SPM), free and open source software for processing neuroimaging data (http://www.fil.ion.ucl.ac.uk/spm/software) running under MATLAB (The MathWorks, Inc., Natick, MA). We used standard steps for processing fMRI data in SPM.[32,33] To control for issues potentially related to scanner stabilization at the start of the scan, the first volume was removed from all runs. For each participant, we first converted data from the raw DICOM format to NIFTI (.nii). We then pre-processed 3D volume image files in SPM, separately for resting-state, speech and social orienting scans. An early preprocessing step ("realignment") by the SPM yielded positional information on the entire original sequence of image volumes during the scan, providing an estimate of original, uncorrected in-scan head motion parameters as a time series. Head motion parameters are the data used in our analyses.

Specifically, the processing yielded six motion parameters (3 linear translations in x, y, z directions in mm corresponding to frontal, sagittal and vertical body axes), and 3 rotations: pitch (about x-axis), roll (about y-axis), and yaw (about z-axis) in degrees.[33]

In the current work we convert volume-to-volume head movements to speed. We focus on angular volume-to-volume speeds defined as the angular difference (delta) between sequential volumes (in three directions x, y, and z) per unit of time, equal to the inter-scan interval (TR). As the angular head rotations were small we combined the speed in all three directions (squaring, summing and then taking the square root) to form one aggregate value of angular speed in deg/second. The speed time series were smoothed using a triangular filter with a width parameter of 5 points (spanning 12.5 s).

Assessing infant intelligence: Samples #1 and #2

Estimation of cognitive abilities in infancy has a long history of careful research. Herein we aim to clarify (*i*) the terminology used in the field from a historical as well as a contemporary perspective, (*ii*) the interpretation of the cognitive composite score on MSEL, and (*iii*) the role of motor abilities in cognitive assessments in general.

The word "intelligence" has been in use since cognitive or intellectual abilities have begun to be studied over 100 years ago in France, by Binet and Simon. This original research investigated mental abilities of young children, not adolescents or adults, which came thereafter. First, at the beginning of the 20th century, Binet and Simon introduced the graded nature of probes that are given on the tests of intelligence (i.e. the "graded scale of intelligence",[75]), such that the items increase in difficulty with the age of children. Second, the word "quotient" in the contemporary term intelligence quotient (IQ) has roots in the term "mental quotient" ("MQ"). MQ is a concept that was developed by Stern in Germany in 1914,[51] also in the context of testing mental faculties in very young children, in order to meaningfully compare scores across ages. In this approach, the mental age is divided by the chronological age because numerically similar values at different chronological ages are not psychologically equivalent.[51] Somewhat later research refers to MQ as ratio intelligence quotient (IQ); moreover, in the 1960s the term "IQ" began to refer to deviation IQs[76]: normalized scores with a fixed mean and standard deviation.

On the MSEL, the Age Equivalent (AE) scores are congruent with the concept of 'intellectual level', and the division by child's chronological age (see next section) is congruent with the concept of Stern's mental quotient and thus produces a ratio IQ. In contrast, the Early Learning Composite (ELC) score is derived using Cognitive T score sum of the four "cognitive"[67] subscales: Expressive Language (EL), Receptive Language (RL), Visual Reception (VR), and Fine Motor (FM). The ELC is a standard, normalized score with mean of 100 and standard deviation of 15, congruent with the concept of deviation IQ. According to Mullen, "measures of general intelligence yield a composite most commonly termed "IQ.""[67] and the ELC as a standard score reflects "a summative measure of *g*",[67] which denotes general intelligence. (Of note, the construct of "*g*" is thought to subsume fluid and crystallized intelligence: fluid intelligence is related to abstract thinking and crystallized intelligence denotes accumulated knowledge through learning.[77]).

The Mullen ELC is strongly and significantly associated[15,78] with the cognitive ability score (GCA), a standard composite score on the Differential Abilities Scales-II (DAS-II; Elliot 2007[79]), which is a more traditional instrument used to assess complex conceptual abilities in children starting at around 2 years of age. The GCA subsumes six subtests that reflect complex conceptual abilities, grouped into verbal ability (word definitions, verbal similarities), nonverbal reasoning ability (matrices, sequential quantitative reasoning), and spatial ability (recall of designs, pattern construction).[79] Moreover, similar to Mullen's ELC, the GCA is a composite measure and "may be viewed as a valid measure of "*g*" " (Elliot 2007; Technical Manual[79]). Importantly, estimates of cognitive abilities on DAS-II ((Elliot, 2007); Technical Manual[79]) have been

validated against Wechsler Preschool & Primary Scale of Intelligence— Third Edition (WPPSI-III)[80] and Wechsler Intelligence Scale for Children— Fourth Edition (WISC-IV).[81]

Despite the long history of research in children's intelligence, there is some disagreement regarding the use of the terms "intelligence" and "IQ". For instance, the DAS-II manual notes that "the terms intelligence and IQ are not used in the DAS-II" (Elliot 2007; Technical manual[79]). However, the words intelligence and IQ *are* in fact widely used by contemporary research studies worldwide that estimate children's cognitive abilities, including the British Twins Early Development Study (TEDS). TEDS uses multiple developmental as well as more traditional IQ assessments to study the construct of intelligence over time in neurotypical children.[82] Moreover, the terms *intelligence* and *IQ* are common in contemporary autism research studies that utilize MSEL (e.g.[54]), including specifically the Mullen's ELC (e.g.[83]) in the US and Canada, respectively.

Lastly, the ELC, while a measure of broader cognitive development and is seemingly independent of movement ability, utilizes T-scores from the Fine Motor domain. Thus, one may wonder about the extent to which motor abilities may contribute to this composite estimate of cognitive abilities. It should be noted that this concern applies to all cognitive abilities assessments or intelligence tests, as well as some clinical assessments including the ADOS. Even tests of fluid intelligence, such as Raven's matrices, require some motor abilities (i.e. for button presses or item selection). For example, while the Raven's Colored Progressive Matrices (RCPM) board form does not require language comprehension or production, or pointing,[84] correct items must still be selected, and this requires some motor ability. Moreover, as noted above, we[15] and others[78] found the Mullen's ELC to highly correlate with the GCA score from DAS-II. While none of the six subtests contributing to GCA include fine motor assessment, at least one of the subtests, 'pattern construction' requires some motor-related abilities. Thus, it may be virtually impossible to completely remove the role of motor contribution to cognitive measures, although the above analysis shows that the ELC has good construct validity as a cognitive composite score. In sum, consistent with the previous research in infant intelligence spanning more than 100 years, herein we use the terms "intelligence" and "IQ" to refer to cognitive abilities in children and specifically to the Mullen's ELC standard score.

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analyses: Main sample (Sample #1)

We used functions in the Statistics and Machine Learning toolbox in MATLAB (MathWorks, Natick, MA, USA) for all statistical analyses. Our interest was in the statistics of the movements. We calculated two measures, coefficient of variance (standard deviation divided by mean) and skewness (normalized third moment). These measures have two important properties. First, they capture the second and third moments of the speed distribution and are intrinsically normalized so as not to depend on the first moment, the mean speed of the movement. That is, these measures do not change with uniform scaling of the speed of the movements. Second, the measures simply depend on the statistic or the samples and do not depend on the order of the samples, allowing us to easily combine data across runs before processing.

The standard calculation of skewness and coefficient of variance are known to be susceptible to outliers. Therefore we have chosen to use standard robust measures of both of these. That is we use Bowley-Galton skewness as a robust measure of skewness and the interquartile range divided by the median as a robust measure of coefficient of variance. The Bowley-Galton Skewness is defined in terms of the first quartile (Q1), the median (Q2), and the third quartile (Q3) and is defined as (Q1 + Q3 - 2 * Q2) / (Q3 - Q1) and we refer to this as IQR skew in the figures.

We calculated these measures of skewness and coefficient of variance separately for each imaging run for a participant and then averaged across runs. This ensures that changes in average speed across runs did not affect the analysis.

Subgroupings by cognitive abilities: Sample #1

We examined the link between movement during sleep and cognitive abilities on the Mullen Scales of Early Learning (MSEL)[67] in infants who received ASD diagnoses in toddlerhood. The Early Learning Composite (ELC) standard score is derived using Cognitive T score sum of the four "cognitive" subscales: Expressive Language (EL), Receptive Language (RL), Visual Reception (VR), and Fine Motor (FM). It is a "summative measure of g"[67] (mean, 100 and standard deviation, 15), and was recently shown to strongly ($r>.8$, $p<0.001$) correlate with another measure of intelligence (DAS-II[15]; in preschool children). In addition, for all infants, verbal DQ (vDQ) (henceforth, verbal intelligence quotient, VIQ) and non-verbal DQ (nvDQ; henceforth, performance intelligence quotient, PIQ) were also computed. The overall DQ as well as VIQ and PIQ are calculated on the basis of Age-Equivalent, AE scores, using a process detailed in Denisova & Lin.[15]

We formed subgroupings of infants (N=111) as a function of cognitive ability on MSEL (lower vs. higher) as follows. For ELC we used 70 as a cut-off (2 SDs below the 100, the standard mean ELC score). To form AE-based scores subgroupings (high vs. low), we used the median score (for VIQ and PIQ, as well as DQ). So as to equalize numbers in the subgroupings as closely as possible, when we split by the median we split any participants on the median into the smaller group. The scores on the MSEL for low and higher ASD subgroupings were (mean $\pm$ sd): DQ_{low}: 61.77$\pm$10.21; DQ_{high}: 91.89$\pm$13.62; ELC_{low}: 58.92$\pm$6.85; ELC_{high}: 87.10$\pm$13.05; VIQ_{low}: 47.16$\pm$12.17; VIQ_{high}: 82.84$\pm$17.96; PIQ_{low}: 74.02$\pm$10.25; PIQ_{high}: 103.33$\pm$11.83.

We used both frequentist (t-test) and Bayesian methods (Bayes Factor) to compare the two measures (c.o.v and skewness) between different groups. A Bayes factor of 1 provides no evidence for a difference, 1-3 anecdotal, 3-10 substantial and 10-30 strong evidence for a difference.[85] Spearman's non-parametric correlation was used to assess the association between cognitive abilities and c.o.v. and skewness measures.

Statistical analyses: Independent sample (Sample #2)

We used both frequentist (t-test) and Bayesian methods (Bayes Factor) to compare the GM measures between different groups. Spearman's non-parametric correlation was used to assess the association between cognitive abilities and GM measures.

Subgroupings by cognitive abilities: Sample #2

As in the main analysis, we formed subgroupings of infants as a function of cognitive ability on MSEL, focusing on full-scale IQ ELC standard score (lower-IQ vs. higher-IQ subgroupings used 70 score as a cut-off on the ELC). For each of the age-bins, GM scores were analyzed between the lower-IQ vs. higher-IQ subgroupings: at 6, 12, 18, 24, and 30 months (all t-tests two-tailed). The average ELC scores (mean $\pm$ sd) at each age bin and for each of the subgroupings are as follows: 6 months, ELC_{low}: 67.12 $\pm$ 4.70; ELC_{high}: 93.56 $\pm$ 11.99; 12 months, ELC_{low}: 64.46 $\pm$ 5.23; ELC_{high}: 93.44 $\pm$ 12.22; 18 months, ELC_{low}: 61.41 $\pm$ 5.56; ELC_{high}: 87.72 $\pm$ 14.33; 24 months, ELC_{low}: 60.01 $\pm$ 6.49; ELC_{high}: 91.39 $\pm$ 14.53; 30 months, ELC_{low}: 56.62 $\pm$ 6.60; ELC_{high}: 87.34 $\pm$ 11.80.