

Appendix 1 to Bussu G, Llera A, Jones EJH, et al. Uncovering neurodevelopmental paths to autism spectrum disorder through an integrated analysis of developmental measures and neural sensitivity to faces. *J Psychiatry Neurosci* 2020.

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Supplemental Material

Uncovering Neurodevelopmental Paths to Autism Spectrum Disorder through an Integrated Analysis of Developmental Measures and Neural Sensitivity to Faces

Bussu G, Llera A., Jones E.J.H., Tye C., Charman T., Johnson M.H., Beckmann C.F.,
Buitelaar, J.K., and the BASIS Team.

Missing Data

Data presented in the current paper were collected as part of a large longitudinal study involving 247 infants recruited in one of two phases of longitudinal assessments (104 in Phase 1 and 143 in Phase 2). Missing data was mainly due to non-attendance to visits. N=10 infants were excluded from this study because they did not receive an ADOS (Autism Diagnostic Observation Schedule) evaluation and/or a clinical outcome evaluation at 36 months. Percentage of complete data and number of infants with missing data by clinical outcome are shown in Table S1. At 24 months, differences between infants with complete and missing data were significant on clinical outcome ($\chi^2(3)=54.2$, $p<1\cdot 10^{-3}$). Differences were

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not significant at other time-points. It is well known in the field that the infant's clinical status can affect data availability through processes like attrition; however, our data provide reasonable evidence to consider the pattern of missing data as "missing at random" (MAR).

To handle missing data at each time-point, we performed imputation through expectation maximization on SPSS (<http://www.ibm.com/analytics/us/en/technology/spss>).

Since our aim was to obtain a longitudinally complete dataset for each infant between 8 and 36 months, infants who did not attend at least one of the visits were excluded from the study (N=5, not significantly different on clinical outcome). Thus, our final sample included 232 infants (161 HR and 71 LR).

ERP task

Infants sat on their parents' laps at a 60 cm distance from a 40 × 29 cm computer screen. The task was the same as in Elsabbagh et al. (2012). It was designed to assess three contrasts within the same group of infants: (1) static face irrespective of gaze direction vs. visual noise stimuli matched on spatial frequency and colour spectra; (2) static faces with direct vs. averted gaze; and (3) dynamic gaze shifts toward vs. away from the infant. The infant gaze during stimulus presentation was recorded by video camera. The visual noise stimuli were constructed from the same faces presented during the face task by randomizing the phase spectra while keeping the amplitude and colour spectra constant. Each trial block began with a static colourful fixation stimulus (subtending approximately 1.6 x 1.6 degrees of visual

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angle) presented for a variable duration between 800 and 1200 ms, followed by a color image of one of four female faces (subtending 21 x 14 degrees of visual angle) with gaze directed either toward or away from the infant. To ensure that infants were fixating the eye region, faces appeared in the center of the screen with the eyes on the same location as the fixation stimuli. In subsequent trials of the same block, the face remained on the screen but displayed three to six gaze shifts, alternating from directed toward to away from the infant. The visual noise stimuli were shown during approximately one third of all blocks, following the fixation stimuli as for faces. Each trial lasted for 1000ms. Trials were presented continuously for as long as the infant remained attentive.

ERP data acquisition and processing

EEG data were recorded using a 128 channel Hydrocel Sensor Net and EGI NetAmps 200 (gain=1000). The montage used was the same as in Elsabbagh et al. (2012). The vertex was used as a reference (Cz in the conventional 10/20 system), and data were digitized with a 500Hz sampling rate and band-pass filtered between 0.1 and 1000 Hz. Data were stored and analysed offline in EGI Netstation 5 using the same protocol as in Elsabbagh et al. (2012). Participants' overall behaviour was initially coded from videotape, and trials were retained only when infants were fixating the centre of the screen at stimulus onset, without any gaze shifts, blinking, or head movements during the segment of chosen duration (800ms in Ph1, and 1000ms in Ph2) following onset of the face stimulus or gaze shift. Data were then corrected to -200ms baseline. Following automatic artefact rejection, an experienced EEG

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researcher visually inspected individual trials. Rejection procedures followed established norms, including removal of segments affected by head, body or eye movement, and including those segments (identified during the video coding procedure) where the infant displayed gaze shifts or looked away from the screen during stimulus presentation. Trials were rejected when data were missing from more than 12 channels, while missing data from 12 or fewer channels were interpolated. Because of variable rates of presentation of each stimulus type, a different number of trials were included for each contrast. Stimulus-locked epochs (-200 to 800ms/1000ms peristimulus window) were averaged for the different contrasts. Visual inspection of the grand average for each condition across the three contrasts revealed characteristic task-dependent infant ERPs over occipital channel groups: P100, N290, and P400. For each contrast, the occipito-temporal channels showing the characteristic waveform were selected, avoiding any particularly noisy channels. The P100, N290, and the P400 were quantified by their amplitude and latency in response to each task.

Measures of early ASD symptoms

To assess ASD symptomatology, the Autism Diagnostic Interview Revised (ADI-R³⁶) was administered at 36 months and the Autism Diagnostic Observation Schedule (ADOS-2³⁷) was administered at 24 and 36 months. Item scores from the ADOS-G were used to calculate ADOS-2 total scores. LR infants from Phase 2 only were administered the ADI-R and the ADOS module 2; while HR siblings from both Phase 1 and Phase 2 were administered the

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ADI-R and the ADOS (n=138 HR were administered module 2 and 23 HR were administered module 1).

Clinical outcome evaluation

The LR group was based on having an older full sibling with typical development. LR infants received no formal clinical diagnoses, but none of them had a community clinical ASD diagnosis at 36 months. In particular, no ADI-R was administered to LR in Phase 1, who did not receive an outcome evaluation. In Phase 2, LR infants were administered the ADOS and ADI-R and received an outcome evaluation at 36 months, but none of them raised any concern for ASD or atypical development. HR siblings received a clinical outcome evaluation at 36 months and were subsequently grouped into siblings with ASD (HR-ASD); with atypical (non-ASD) development (HR-Atypical); and with typical development (HR-Typical).

Expert clinical researchers reviewed all available information at 24 months and 36 months and assigned clinical consensus best estimate diagnosis of ASD according to ICD-10 (World Health Organization 1993) or DSM-5 criteria (American Psychiatric Association 2013), depending on the phase of the study. The best estimate diagnoses for the two phases were reviewed for differences in categorization and considered to be similar. Among high-risk infants who did not meet criteria for ASD, a subgroup of siblings was classified as ‘atypical’ based on having: ADOS and/or ADI-R above ASD threshold, and/or MSEL more than 1.5

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standard deviations below average on visual reception (VR) and/or receptive language (RL) and/or expressive language (EL) and/or early learning composite (ELC).

Among infants included in the final longitudinal sample, 32/161 [19.9%] high-risk siblings were categorized as HR-ASD; 43/161 [26.7%] high-risk siblings were categorized as HR-Atypical; and 86/161 [53.42%] high-risk siblings were categorized as HR-Typical. The breakdown of HR-Atypical infants based on criteria for “atypical” development is shown in Table S2.

In the subsample included in the multimodal analysis, 30/140 [21.4%] high-risk siblings were categorized as HR-ASD, 36/140 [25.7%] high-risk siblings were categorized as HR-Atypical, and 74/140 [52.9%] high-risk siblings were categorized as HR-Typical. The breakdown of HR-Atypical infants based on criteria for “atypical” development is shown in Table S2.

Association between processes identified across analyses

To test the link between the identified components from the multimodal analysis and the longitudinal analysis, we correlated the behavioural score maps of IC7 (excluding gross motor scores) and of IC1 and IC3 at 8 months (Figure 2B versus Figure 3A column 1, and Figure 3E column 1 in the main text). Results showed a significant correlation between IC1 and IC7 ($r=0.92$, $p<0.001$).

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Table S1. Missing data. This table the number of infants attending each visit (n/n_{total}), where $n_{total}=237$ is the total number of infants after excluding infants who did not receive a clinical evaluation and/or an ADOS classification at 36 months; the percentage of complete data by clinical instrument at each visit; the number of subjects with missing data by clinical outcome at each visit.

Visit	Attendance (n/n_{total})	Complete data (%)			Subjects with missing data (n)			
		MSEL	VABS	AOSI/ADOS	LR	HR-Typical	HR-Atypical	HR-ASD
8 months	237/237	99.6	97.9	100	2	3	0	1
14 months	234/237	99.2	96.2	100	4	4	2	1
24 months	235/237	82.7	97.0	80.2	48	11	13	5
36 months	237/237	99.2	97.9	100	2	1	2	2

Abbreviations: ASD= autism spectrum disorder; MSEL= Mullen Scales of Early Learning; VABS = Vineland Adaptive Behavior Scales; AOSI= Autism Observation Scale for Infants; ADOS= Autism Diagnostic Observation Schedule; HR = high-risk siblings; LR = low-risk controls.

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Table S2. HR-Atypical criteria. This table shows the number of infants among HR-Atypical siblings ($n/n_{HR-Atypical}$) who meet specific criteria for “atypical” development for the different samples included in the two separate analyses.

	MSEL criterion				ADOS	ADI-R	ADOS & ADI-R	ADOS & MSEL	ADI-R & MSEL
	VR	RL	EL	ELC	criterion	criterion	criterion	criterion	criterion
Longitudinal Analysis	9/43	14/43	9/43	14/43	30/43	6/43	4/43	7/43	1/43
Multimodal Analysis	8/36	11/36	8/36	10/36	27/36	5/36	4/36	6/36	1/36

Abbreviations: ASD= autism spectrum disorder; MSEL= Mullen Scales of Early Learning; VR= visual reception (MSEL); RL= receptive language (MSEL); EL= expressive language (MSEL); ELC = early learning composite score (MSEL); ADOS= Autism Diagnostic Observation Schedule; ADI-R = Autism Diagnostic Interview-Revised; HR = high-risk siblings.

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Table S3. Clinical characteristics of the sample included in the multimodal analysis

	MSEL					VABS			AOSI	
	GM	FM	VR	RL	EL	Comm	DL	Mot	Soc	Total score
LR (n=61)	49.49 (8.42)	57.21 (10.11)	55.48 (9.73)	47.72 (8.77)	51.90 (9.21)	100.1 (13.24)	100.85 (12.87)	94.85 (13.49)	101.38 (12.16)	6.36 (3.91)
HR-Typ (n=74)	46.86 (10.52)	55.91 (12.77)	54.42 (11.95)	49.53 (10.14)	50.20 (10.22)	96.16 (15.75)	100.85 (13.68)	89.86 (16.24)	99.97 (12.51)	8.82 (4.75)
HR-Atyp (n=36)	43.44 (12.58)	51.67 (12.76)	51.42 (11.51)	45.14 (8.80)	51.69 (11.43)	91.83 (15.40)	100.08 (11.22)	79.67 (15.95)	98.69 (10.45)	9.53 (4.86)
HR-ASD (n=30)	42.82 (10.47)	47.80 (11.97)	50.46 (9.32)	42.80 (12.23)	49.82 (11.83)	89.77 (15.73)	93.17 (15.42)	84.17 (16.26)	96.87 (16.18)	10.90 (5.52)

Note: This table shows measures [mean (standard deviation, SD)] at 8 months from standardized clinical instruments by clinical outcome group.

Abbreviations: ASD= autism spectrum disorder; MSEL= Mullen Scales of Early Learning; GM= gross motor abilities (MSEL); FM= fine motor abilities (MSEL); VR= visual reception (MSEL); RL= receptive language (MSEL); EL= expressive language (MSEL); VABS = Vineland Adaptive Behavior Scales; Comm = communication skills (VABS); DL = daily living skills (VABS); Soc = social skills (VABS); Mot = motor skills (VABS); AOSI= Autism Observation Scale for Infants; HR = high-risk siblings; LR = low-risk controls.

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Table S4. Clinical characteristics of the longitudinal sample

	Overall (n=232)				High-Risk (n = 161)								Low-Risk (n = 71)							
					ASD (n = 32)				Atypical (n = 43)				Typical (n = 86)							
	8 m	14 m	24 m	36 m	8 m	14 m	24 m	36 m	8 m	14 m	24 m	36 m	8 m	14 m	24 m	36 m	8 m	14 m	24 m	36 m
MSEL																				
GM	47.24 (10.68)	49.57 (14.79)	51.54 (11.50)	-	43.84 (11.37)	45.59 (14.46)	46.95 (14.02)	-	45.07 (12.57)	47.60 (13.01)	49.46 (10.60)	-	47.31 (10.48)	50.87 (14.97)	50.91 (11.39)	-	50.00 (8.68)	50.97 (15.54)	55.65 (9.72)	-
FM	55.10 (12.41)	55.69 (9.95)	48.77 (10.67)	51.40 (16.39)	48.53 (12.91)	50.50 (11.63)	44.64 (11.55)	39.84 (16.09)	52.00 (12.78)	52.63 (11.07)	45.17 (13.30)	43.30 (16.01)	56.77 (12.71)	56.50 (8.43)	48.49 (8.95)	54.34 (14.80)	57.9 (10.17)	58.89 (8.83)	53.15 (8.83)	57.96 (14.02)
VR	53.81	49.99	53.62	56.83	51.59	45.09	47.30	49.29	50.49	48.53	46.92	49.47	54.35	48.95	55.18	60.51	56.17	54.35	58.65	60.21

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	(11.07)	(9.98)	(12.85)	(13.82)	(10.46)	(9.31)	(13.08)	(17.54)	(11.16)	(9.56)	(13.62)	(15.04)	(11.75)	(9.96)	(10.59)	(10.88)	(9.95)	(9.05)	(12.14)	(11.29)
RL	47.56	42.64	52.17	52.53	43.35	36.19	41.71	43.47	46.05	40.19	46.92	43.37	49.90	43.68	53.26	55.80	47.55	45.77	58.75	58.21
	(10.17)	(11.90)	(12.99)	(12.85)	(12.50)	(9.05)	(15.47)	(17.71)	(8.70)	(10.73)	(13.17)	(13.04)	(10.08)	(12.31)	(10.74)	(8.37)	(9.33)	(12.01)	(9.71)	(9.15)
EL	51.05	47.77	51.60	53.95	50.08	42.13	46.23	43.28	51.26	44.98	47.72	45.20	50.52	49.64	50.70	57.76	52.01	49.75	57.46	59.39
	(10.21)	(10.66)	(12.93)	(12.86)	(11.89)	(11.44)	(15.30)	(16.14)	(11.00)	(10.90)	(13.20)	(12.31)	(10.14)	(9.93)	(11.49)	(9.33)	(9.07)	(9.93)	(11.18)	(9.38)
VABS																				
Comm	95.73	96.59	103.31	101.12	90.19	86.04	94.47	88.96	89.53	93.17	98.41	93.18	96.35	98.35	104.31	103.26	101.23	101.29	109.06	108.82
	(15.88)	(13.30)	(12.73)	(14.28)	(15.33)	(14.28)	(15.06)	(18.19)	(17.12)	(15.85)	(10.78)	(14.03)	(15.71)	(11.63)	(10.66)	(10.24)	(13.58)	(9.68)	(11.88)	(10.42)
DL	99.95	95.17	105.48	103.06	93.56	85.63	97.88	88.36	98.98	93.38	101.49	97.74	101.24	96.58	107.55	106.63	101.87	98.86	108.83	108.60
	(13.49)	(12.99)	(12.48)	(13.03)	(15.28)	(13.39)	(13.95)	(18.03)	(11.75)	(13.38)	(13.50)	(12.64)	(13.14)	(12.62)	(11.09)	(8.84)	(13.39)	(10.80)	(10.80)	(7.91)
Mot	89.65	100.33	99.97	93.66	85.13	98.06	98.19	84.66	80.65	95.73	96.51	86.47	90.73	100.40	99.50	95.79	95.84	104.04	103.44	99.49

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	(16.21)	(12.84)	(10.66)	(12.23)	(16.71)	(14.27)	(12.49)	(13.25)	(15.66)	(15.10)	(11.83)	(10.48)	(15.88)	(11.59)	(10.09)	(10.35)	(13.80)	(11.15)	(8.77)	(10.54)
Soc	99.84	97.77	100.72	97.78	96.97	91.40	88.91	79.64	97.93	96.53	97.33	92.43	99.62	98.44	101.99	100.93	102.55	100.58	106.56	105.38
	(12.72)	(11.66)	(11.46)	(12.89)	(15.66)	(11.78)	(11.68)	(12.66)	(11.52)	(12.66)	(10.65)	(11.75)	(11.85)	(11.06)	(8.21)	(8.68)	(12.71)	(10.71)	(10.74)	(8.00)
AOSI	8.34	5.10			10.66	7.59			9.47	7.05			8.51	4.48			6.39	3.56		
	(4.86)	(4.34)			(5.71)	(4.42)			(4.86)	(4.94)			(4.66)	(3.98)			(3.96)	(3.41)		
ADOS			5.04	5.75			11.25	10.63			6.67	8.95			4.13	3.06			2.35	4.89
			(5.04)	(4.84)			(5.59)	(6.54)			(5.07)	(4.95)			(3.72)	(2.04)			(3.16)	(3.42)

Note: This table shows measures [*mean (standard deviation, SD)*] from standardized clinical instruments by clinical outcome group.

Abbreviations: ASD= autism spectrum disorder; MSEL= Mullen Scales of Early Learning; GM= gross motor abilities (MSEL); FM= fine motor abilities (MSEL); VR= visual reception (MSEL); RL= receptive language (MSEL); EL= expressive language (MSEL); VABS = Vineland Adaptive Behavior Scales; Comm = communication skills (VABS); DL = daily living skills (VABS); Soc = social skills (VABS); Mot = motor skills (VABS); AOSI= Autism Observation Scale for Infants; ADOS= Autism Diagnostic Observation Schedule; HR = high-risk siblings; LR = low-risk controls.

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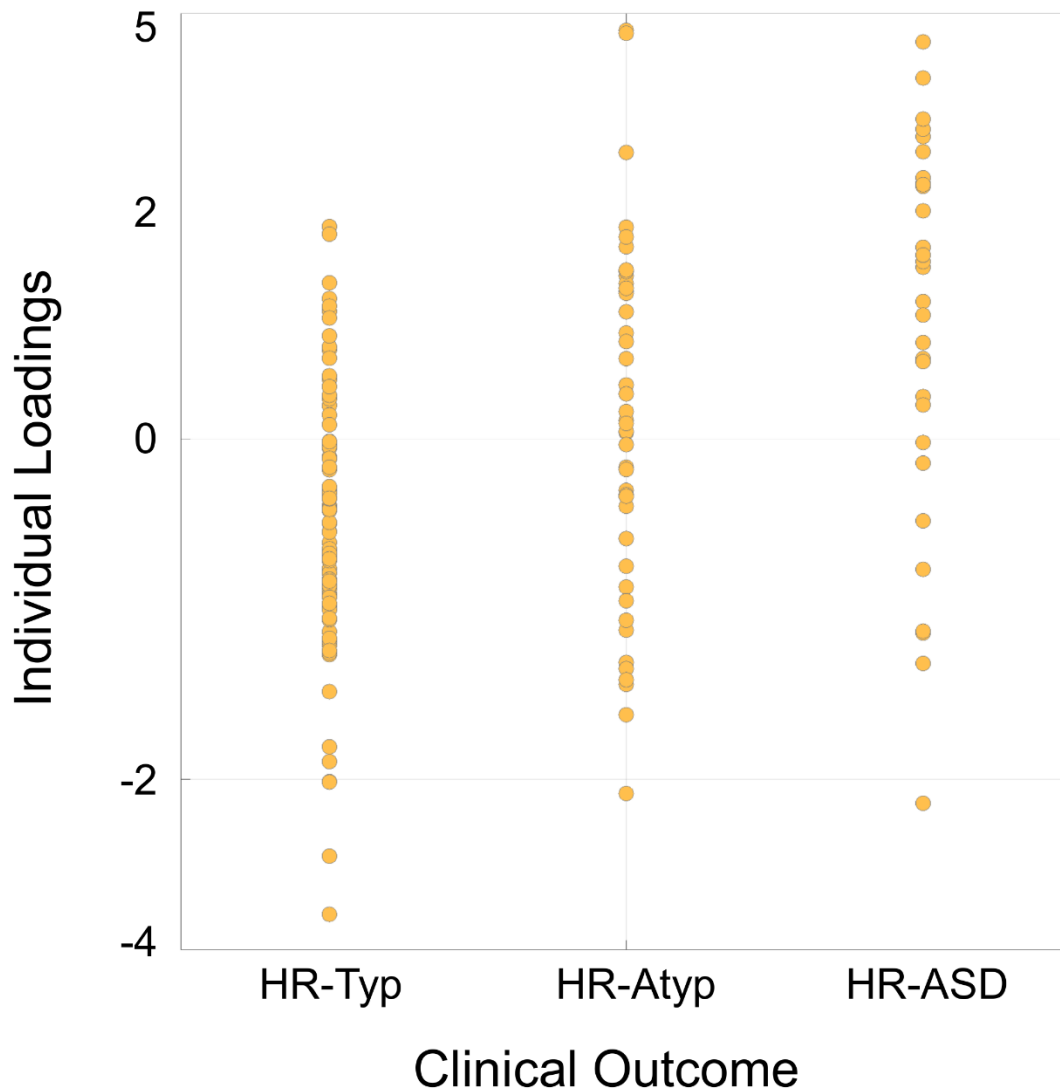


Figure S1. Association between individual loadings on IC3 and clinical outcome among

HR siblings. This figure shows individual participant loadings to the component IC3

obtained from the analysis of longitudinal clinical data grouped by clinical outcome at 36

months among HR siblings only. We excluded LR siblings to show the linear relationship

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between component loadings and clinical outcome among HR siblings ($\beta=0.33$, $p=2.26 \cdot 10^{-10}$), with increasing individual loadings going from HR-Typical to HR-ASD siblings on this component indicating a stagnation in cognitive development after 24 months of age.

Abbreviations: ASD = autism spectrum disorder; HR = infant at high familial risk for ASD; LR = infant at low familial risk for ASD.

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