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Supplementary Materials for

Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age

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Supplementary Materials:

Materials and Methods

Whole-brain visualization

To visualize functional connections that likely contribute to the accuracy of this classification approach, each pair of ROIs that were used in each of the nested feature sets (100% consensus) are projected onto a Talairach brain in Figure 2 in the Main Text. The Talairach coordinates and average connectivity values by group for these regions are listed in Table S1.

Individual classification accuracy

Since the primary goal is diagnostic classification for individuals, we also measured the individual classification accuracy, following Greene *et al.* (*57*), to understand how reliably each infant was classified across the nested models. This analysis determines the rate at which each of the 59 individuals is classified accurately by testing an SVM classifier created from each of the nested sets used in the primary analysis. This analysis is akin to a leave-two-out-cross-validation method in which one participant (test case) is removed while the remaining participants underwent the LOOCV procedure. Each nested set is trained on a slightly different training set, allowing the test case to be classified with 57 separate models. The test case is then tested on each of those models, and an average individual accuracy was calculated for that case. Once repeated using each participant as a test case, individual accuracy can be measured for each individual, reflecting how reliably that participant is classified across models. These results are shown in figure S1.

Comparison to independent high-risk sample

In order to ensure that our sample of high-risk infants was representative of the general population of high-risk individuals, we compared the 24-month behavioral scores from our sample of infants to scores from an independent sample of high-risk infants. The comparison group is made up of 68 participants that were collected as part of the Infant Brain Imaging Study, but were not included in the main analysis because they did not complete a 6-month MRI visit. This group consisted of 20 ASD-pos and 48 ASD-neg 24-month-old participants. Unpaired t-tests were used to assess between-groups differences on scores from the RBS-R, MSEL, and CSBS. These results are presented in Table S2. Overall, these results suggest that there are no apparent differences between the high-risk sample used in our main analysis and this additional independent sample of high-risk infants. This supports the conclusion that our classifier results are likely to generalize to other high-risk infants.

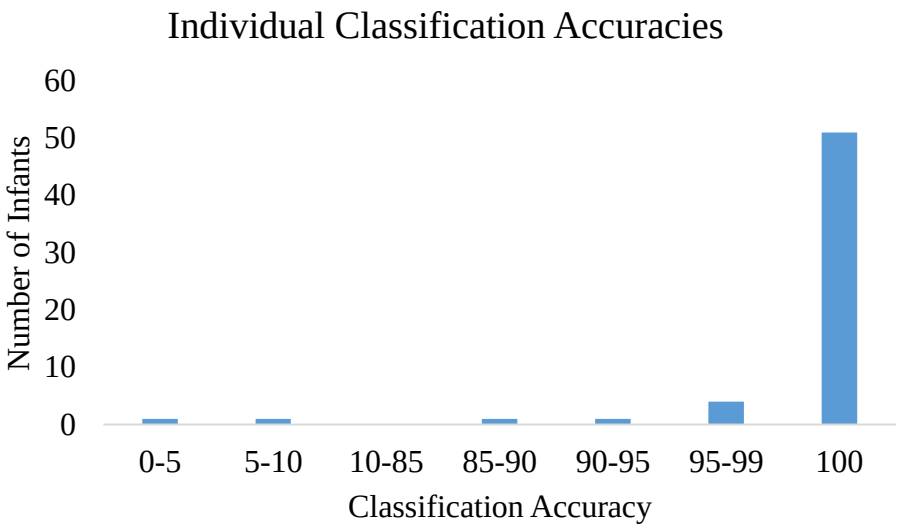

Fig. S1. Individual classification accuracies.

Each participant's individual classification accuracy was calculated with a model built from each of the nested classifiers.

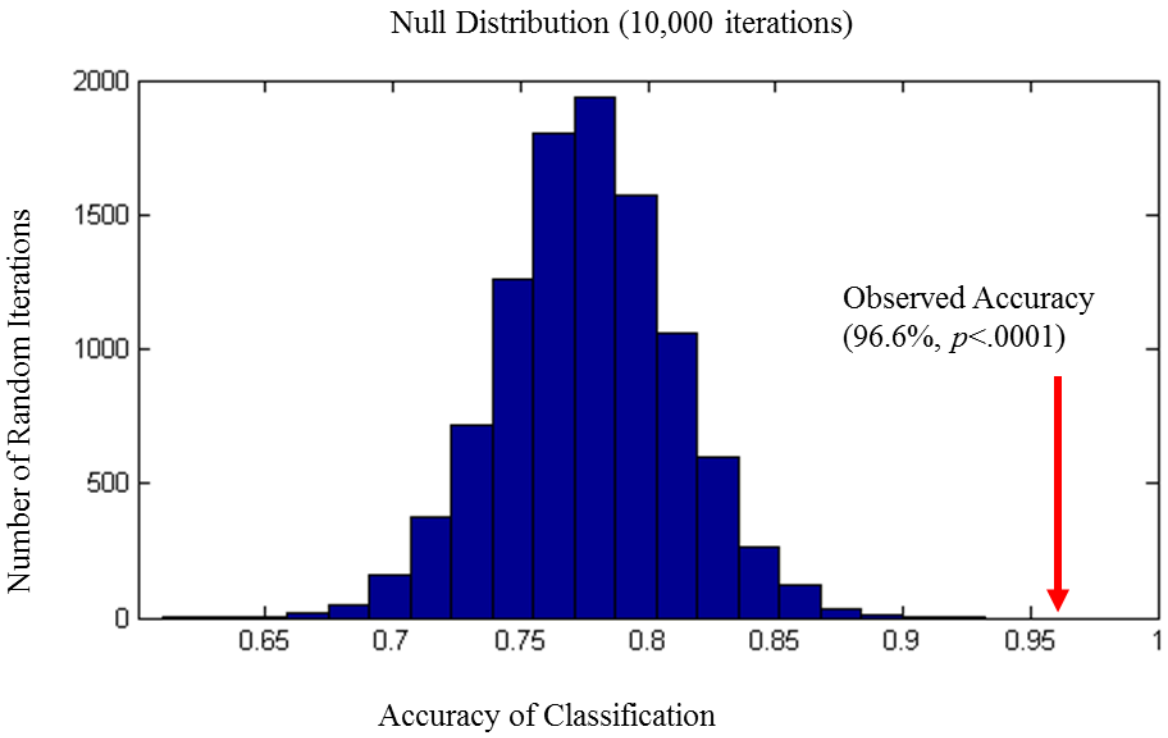

Fig. S2. Null distribution of classification accuracy.

The blue bars represent the number of random iterations at each level of accuracy. The red arrow marks the observed accuracy from the nested leave-one-out cross-validation classification analysis, corresponding to a *p*-value of $p<.0001$.

Table S1. The Talairach coordinates for each of the ROIs.

The regions are shown in Figure 2 (*Main Text*) are listed, along with the average Fisher z-transformed functional connectivity *r*-value for each group.

	ROI 1			ROI 2			Average r-value			
	X	Y	Z	X	Y	Z	ASD-pos	ASD-neg	*t*-value	*p*-value
CSBS	46	-45	44	-52	-25	41	0.391	0.132	-3.0963	0.003
	-50	0	-24	8	-48	69	0.113	-0.062	-2.9325	0.0048
	-21	4	-2	8	-48	69	-0.261	-0.019	4.3423	0.0001
	-48	-66	-8	51	-31	34	0.357	0.137	-3.2171	0.0021
	-43	-65	31	-47	-28	5	-0.135	0.054	2.9743	0.0043
	-9	10	10	-47	-28	5	0.109	-0.069	-3.6864	0.0005
	-33	49	9	-51	-24	22	0.132	-0.059	-3.1777	0.0024
	-11	-93	-15	-3	-50	12	-0.231	-0.034	3.0045	0.0039
	56	-8	-2	11	30	24	0.116	-0.081	-3.2679	0.0018
	26	-39	-11	50	-6	-12	0.236	0.008	-3.6447	0.0006
	-25	-89	0	44	-52	28	0.153	-0.043	-2.9257	0.0049
	20	-70	-9	-47	-43	0	0.102	-0.138	-3.9104	0.0002
	-47	-9	-36	17	-48	-9	0.091	-0.111	-3.6725	0.0005
	39	-5	48	19	-66	1	-0.192	0.003	3.1196	0.0028
	39	-5	48	-17	-68	3	-0.205	-0.043	3.023	0.0037
	39	-39	-20	26	4	-4	-0.249	-0.069	3.0731	0.0032
MSEL	-41	-56	41	26	-96	-15	-0.120	0.059	2.9743	0.0043
	4	18	39	26	-96	-15	0.039	-0.108	-3.0157	0.0038
	29	49	20	53	-33	-14	0.248	0.027	-3.0839	0.0031
	-26	-71	33	-8	-54	57	0.347	0.152	-3.0113	0.0039
	17	-79	-34	-52	-25	41	-0.125	0.078	2.9314	0.0048
	52	-47	36	-52	-25	41	0.162	-0.065	-3.7255	0.0004
	-10	-21	8	-44	-34	44	-0.207	-0.046	2.9882	0.0041
	11	-20	9	-44	-34	44	-0.247	-0.055	3.8033	0.0004
	-40	40	2	51	-31	34	0.293	0.039	-3.4717	0.001
	-48	-66	-8	51	-31	34	0.357	0.137	-3.2171	0.0021
	14	-64	24	62	-36	21	0.157	-0.033	-2.9463	0.0047
	-44	-61	18	-47	-28	5	-0.059	0.189	4.1552	0.0001
	-43	-65	31	-47	-28	5	-0.135	0.054	2.9743	0.0043
	-48	-66	-8	56	-21	30	0.237	0.039	-3.1136	0.0029
	-8	-80	5	-29	-29	12	0.135	-0.029	-3.2171	0.0021
	-14	-72	-9	-29	-29	12	0.155	-0.026	-3.5678	0.0007
	-30	-14	1	-29	-29	12	0.402	0.106	-4.5618	<.0001
	-10	-21	8	-39	-75	22	-0.001	-0.192	-3.1934	0.0023
	-4	21	46	-43	-65	31	0.084	-0.090	-2.9371	0.0048
	-11	-93	-15	-3	-50	12	-0.231	-0.034	3.0045	0.0039
	19	-85	-4	14	-64	24	-0.159	0.049	3.1065	0.0029
	19	-85	-4	28	-76	-31	0.223	0.005	-3.4512	0.0011
	22	-58	-22	-44	27	-9	-0.221	-0.032	3.1342	0.0027
	39	-5	48	23	39	-9	0.168	-0.039	-3.4365	0.0011
	39	-5	48	32	48	-6	0.154	-0.014	-3.3451	0.0015
	23	-60	57	39	-5	48	0.243	-0.047	-4.043	0.0002
	26	-9	54	-10	-21	8	-0.246	-0.028	3.2268	0.0021
	-53	-41	12	27	-3	7	0.095	-0.099	-2.9981	0.004
	20	-70	-9	-47	-9	-36	0.045	-0.145	-3.1499	0.0026
RBS-R	32	33	-6	-23	-96	-15	-0.106	0.105	2.9824	0.0042
	5	3	51	26	-96	-15	0.062	-0.098	-2.9271	0.0049
	-41	-56	41	26	-96	-15	-0.120	0.059	2.9743	0.0043
	-4	21	46	26	-96	-15	0.084	-0.085	-2.9766	0.0043
	4	18	39	26	-96	-15	0.039	-0.108	-3.0157	0.0038
	29	49	20	53	-33	-14	0.248	0.027	-3.0839	0.0031
	-25	-89	0	32	33	-6	-0.135	0.122	3.6749	0.0005
	19	-85	-4	-8	-54	57	-0.256	-0.028	3.885	0.0003
	-26	-71	33	-8	-54	57	0.347	0.152	-3.0113	0.0039
	-40	40	2	-52	-25	41	0.261	0.026	-3.1149	0.0029
	-21	4	-2	8	-48	69	-0.261	-0.019	4.3423	0.0001
	-30	-14	1	8	-48	69	-0.324	-0.112	3.7371	0.0004
	52	-47	36	-39	-22	52	-0.005	-0.193	-3.1362	0.0027
	-27	-79	16	26	-42	57	0.114	-0.107	-3.0675	0.0033
	-41	20	31	47	-24	42	0.143	-0.047	-2.9331	0.0048

-10	-21	8	-44	-34	44	-0.207	-0.046	2.9882	0.0041
11	-20	9	-44	-34	44	-0.247	-0.055	3.8033	0.0004
-48	-66	-8	51	-31	34	0.357	0.137	-3.2171	0.0021
-40	-60	-10	47	4	3	0.074	-0.111	-3.3945	0.0013
5	60	3	-33	0	6	-0.292	-0.098	3.4086	0.0012
27	-3	7	62	-36	21	0.088	-0.098	-3.1735	0.0024
-9	10	10	-58	-27	13	0.097	-0.092	-3.0845	0.0031
-14	-72	-9	-47	-28	5	0.144	-0.017	-3.1967	0.0023
-9	10	10	-47	-28	5	0.109	-0.069	-3.6864	0.0005
-33	49	9	-51	-24	22	0.132	-0.059	-3.1777	0.0024
-40	40	2	-51	-24	22	0.269	0.013	-3.5744	0.0007
-3	36	20	-53	-12	12	0.138	-0.061	-3.2215	0.0021
-23	-90	15	-53	-12	12	0.079	-0.124	-3.3904	0.0013
-33	49	9	56	-21	30	0.161	-0.038	-3.2002	0.0022
-8	-80	5	-29	-29	12	0.135	-0.029	-3.2171	0.0021
22	6	5	-29	-29	12	0.227	0.049	-2.9249	0.0049
-30	-14	1	-29	-29	12	0.402	0.106	-4.5618	<.0001
-23	-90	15	-39	-75	22	-0.141	0.117	3.1456	0.0026
-30	-14	1	5	60	3	-0.229	-0.040	3.3357	0.0015
-53	-41	12	8	42	-9	0.212	0.027	-2.9973	0.004
-41	9	-30	-17	57	-3	0.132	-0.107	-3.5593	0.0008
51	-45	22	-44	-61	18	0.142	0.399	3.5378	0.0008
49	-31	-2	-44	-61	18	0.130	0.344	3.2382	0.002
-26	-71	33	-44	-61	18	0.249	0.036	-3.0366	0.0036
-17	-68	3	-41	9	-30	0.145	-0.072	-3.5503	0.0008
36	37	20	44	12	-24	-0.003	-0.197	-3.0982	0.003
50	3	-24	-55	-27	-14	0.224	0.439	2.9337	0.0048
56	-54	-12	26	12	-12	0.064	-0.098	-2.9917	0.0041
50	27	6	5	-60	33	0.141	-0.029	-3.4505	0.0011
8	-72	9	-3	-50	12	-0.175	0.045	3.0276	0.0037
6	-81	4	-3	-50	12	-0.237	-0.012	3.4234	0.0012
19	-66	1	-3	32	39	-0.293	-0.118	3.2029	0.0022
24	43	31	11	30	24	-0.042	0.178	3.0643	0.0033
56	-8	-2	11	30	24	0.116	-0.081	-3.2679	0.0018
26	-39	-11	50	-6	-12	0.236	0.008	-3.6447	0.0006
19	-85	-4	28	-76	-31	0.223	0.005	-3.4512	0.0011
20	-70	-9	-47	-43	0	0.102	-0.138	-3.9104	0.0002
56	-8	-2	-7	-72	38	-0.192	-0.033	3.0628	0.0033
-29	-12	-33	10	-67	39	-0.264	-0.061	3.2248	0.0021
49	-31	-2	8	-90	-9	0.155	-0.044	-3.2011	0.0022
19	-85	-4	17	-90	-15	0.654	0.408	-3.1895	0.0023
-47	-9	-36	17	-48	-9	0.091	-0.111	-3.6725	0.0005
39	-5	48	19	-66	1	-0.192	0.003	3.1196	0.0028
12	-78	38	-23	-90	15	-0.057	0.197	3.2124	0.0022
32	48	-6	-17	-68	3	-0.205	-0.027	3.109	0.0029
39	-5	48	-17	-68	3	-0.205	-0.043	3.023	0.0037
32	48	-6	-15	-53	-2	-0.237	-0.042	3.0124	0.0039
-53	-41	12	-15	-53	-2	0.166	-0.023	-2.9303	0.0049
-38	-87	-9	25	-79	-16	0.433	0.164	-3.7706	0.0004
49	-35	9	25	-79	-16	0.071	-0.102	-3.0357	0.0036
44	-60	4	-3	-81	18	0.183	-0.029	-3.096	0.003
35	-84	11	-38	-87	-9	0.370	0.109	-3.4985	0.0009
26	-9	54	-25	-89	0	0.132	-0.063	-3.1446	0.0026
24	43	31	-31	-78	-15	-0.216	-0.033	3.2775	0.0018
22	-58	-22	-51	-50	39	-0.036	-0.213	-3.2502	0.0019
39	-5	48	32	48	-6	0.154	-0.014	-3.3451	0.0015
39	-5	48	-41	33	24	0.277	-0.031	-4.3877	0.0001
-32	-48	44	39	-5	48	0.218	-0.030	-3.7165	0.0005
-32	-48	44	11	-20	9	-0.317	-0.145	3.6126	0.0006
39	-39	-20	-21	4	-2	-0.279	-0.070	3.4365	0.0011
-53	-41	12	-30	-14	1	0.077	-0.116	-3.3052	0.0016
20	-70	-9	-47	-9	-36	0.045	-0.145	-3.1499	0.0026
39	-39	-20	26	4	-4	-0.249	-0.069	3.0731	0.0032

Table S2. Comparison to independent high-risk sample.

Averages are broken down in each cohort between high-risk infants who went on to have ASD (ASD-pos) and those who did not (ASD-neg) for both the primary cohort (left panel) and the additional cohort (middle panel). The right panel, the group averages of the two cohorts are compared using t-tests between the ASD-neg as well for the ASD-pos subsets of infants from each cohort. These averages were compared using a two-sample t-test, corrected for unequal sample size. None of the *p*-values are significant (all $p>0.07$).

		Averages						t-tests			
								ASD-neg		ASD-pos	
		Primary Cohort	ASD-pos	ASD-Neg	New Cohort	ASD-pos	ASD-Neg	*t-value*	*p-value*	*t-value*	*p-value*
CSBS	**Social Interaction**	2.14	0.75	2.40	2.33	1.05	2.28	0.48	0.71	0.91	0.12
CSBS	**Joint Attention**	3.30	1.63	3.62	3.20	1.88	3.72	0.43	0.80	0.47	0.73
MSEL	**Expressive Language**	20.98	19.30	21.34	21.41	17.30	23.13	0.80	0.26	0.75	0.33
MSEL	**Fine Motor**	24.10	24.09	24.11	23.97	21.90	24.83	0.60	0.53	0.89	0.14
MSEL	**Gross Motor**	25.89	24.90	26.12	25.15	23.26	25.93	0.66	0.45	0.95	0.07
MSEL	**Receptive Language**	23.35	20.80	23.89	23.25	16.50	26.06	0.43	0.79	0.90	0.13
MSEL	**Visual Reception**	26.74	24.55	27.26	27.74	23.35	29.56	0.38	0.88	0.69	0.40
RBS-R	**Stereotyped**	0.91	3.44	0.32	1.22	2.93	0.54	0.80	0.26	0.48	0.71
RBS-R	**Self-Injurious**	0.64	1.89	0.34	0.84	1.71	0.49	0.60	0.53	0.39	0.87
RBS-R	**Compulsive**	0.96	3.44	0.37	0.80	1.29	0.60	0.66	0.45	0.82	0.23
RBS-R	**Ritualistic**	0.79	2.22	0.45	0.67	1.07	0.51	0.43	0.79	0.65	0.45
RBS-R	**Sameness**	1.60	4.89	0.82	1.43	3.07	0.77	0.38	0.88	0.65	0.45
RBS-R	**Restricted**	0.47	1.89	0.13	0.86	1.93	0.43	0.81	0.24	0.34	0.97