

Appendix 1 to Wolfers T, Arenas AL, Onnink AMH, et al. Refinement by integration: aggregated effects of multimodal imaging markers on adult ADHD. *J Psychiatry Neurosci* 2017.

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Methods: Supplementary Table 1

Prior to statistical association we exclude imaging markers that were associated with confounds and are listed below. In subsequent sensitivity analyses we included those markers to the analyses and showed that it remained robust Supplementary Table 4.

Supplementary Table 1: Excluded imaging markers

Excluded imaging marker	<i>Reason for exclusion</i>	<i>Evidence for exclusion</i>
M2	<i>Affected by differences in diffusion acquisition protocols</i>	$p = <.001; \eta^2 = .938$
M7	<i>Affected by differences in diffusion acquisition protocols</i>	$p = .042; l \eta^2 = .023$
M9	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M10	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M11	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M12	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M13	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M16	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M24	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M28	<i>Affected by differences in diffusion acquisition protocols</i>	$p = .033; \eta^2 = .025$
M39	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M41	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M42	<i>Variance explained by a single participant</i>	<i>Variance explained > 10%</i>
M= imaging marker		

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Methods: Supplementary Table 2

Details of the full logistic regression model as reported in the results section and Figure 1 and 2.

Supplementary Table 2: Logistic regression on adult ADHD

<i>N=180</i>	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>Accuracy</i>	<i>p</i>
<i>Descriptive logistic regression</i>	143	36	27.86%	75.50%	.004**
	<i>Cross validation</i>	-			<i>Perm. p</i>
<i>Predictive logistic regression</i>	LOO-CV	-		60.00%	<.001**
<i>Individual markers</i>	<i>Regression coefficient</i>	<i>z-stats</i>			<i>p</i>
M6	.762	3.242			.001**
M19	.698	3.236			.001**
M32	.506	2.258			.024*
M1	-.542	-2.196			.028*
M38	-.454	-2.171			.030*
M47	-.497	-1.968			.049*
M17	.370	1.907			.056
M15	.361	1.742			.081
M31	-.331	-1.676			.094
M4	-.331	-1.612			.107
M18	-.315	-1.539			.124

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M45	-.313	-1.473	.141
M20	.284	1.435	.151
M22	.261	1.309	.191
M36	-.227	-1.144	.252
M3	-.235	-1.123	.261
M27	-.197	-1.023	.306
M43	.178	.918	.359
M40	.170	.818	.413
M8	.194	.785	.433
M23	-.151	-.755	.451
M26	-.149	-.744	.457
M35	-.149	-.713	.476
M44	.136	.705	.481
M21	-.122	-.624	.533
M34	-.109	-.543	.587
M37	-.092	-.437	.662
M30	-.084	-.422	.673
M50	-.084	-.414	.679
M14	-.068	-.356	.722
M33	-.059	-.304	.761

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M5	-.065	-.298	.765
M49	-.050	-.240	.810
M29	.048	.233	.816
M48	-.032	-.175	.861
M25	-.032	-.170	.865
M46	-.022	-.113	.910

ADHD= Attention-deficit/hyperactivity disorder; df. = Degrees of freedom; p = uncorrected p-value; Perm. p = p-value using permutation testing; LOO-CV = Leave one participant out cross-validation method
 * Nominal significant (p<.05)
 ** Overall regression model that remains significant after multiple comparisons using the Bonferroni-Holm method p< (.05/4) or an individual regressor that remains significant after multiple comparison correction p < (.05/37). The thresholds are determined based on the number of independent regressions (adult ADHD, estimated intelligence, age and gender) or the number of predictors in each individual model (37 Imaging Markers).

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Methods: Supplementary Table 3

Sensitivity analysis with estimated intelligence, age and gender as part of the main logistic regression on adult ADHD. Detailed overview of the model

Supplementary Table 3: Logistic regression on adult ADHD with estimated intelligence, age and gender

<i>N=180</i>	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>Accuracy</i>	<i>p</i>
<i>Descriptive logistic regression</i>	140	39	29.73%	77.20%	<.001**
	<i>cross validation</i>	-		<i>Accuracy</i>	<i>Perm. p</i>
<i>Predictive logistic regression</i>	LOO-CV	-		60.50%	.002**
<i>Individual regressors</i>	<i>Regression coefficient</i>	<i>z-stats</i>			<i>p</i>
M6	.742	3.081			.002*
M19	.677	2.996			.003*
M1	-.882	-2.923			.003*
M38	-.522	-2.401			.016*
M32	.499	2.193			.028*
M4	-.459	-2.042			.041*
age	-.837	-1.991			.047*
M47	-.449	-1.729			.083
M31	-.349	-1.727			.084
M15	.347	1.647			.099
M45	-.357	-1.626			.104

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M3	-.407	-1.471	.141
M22	.295	1.383	.167
M36	-.272	-1.328	.184
M17	.260	1.280	.200
M35	-.317	-1.279	.201
M20	.218	1.063	.288
M40	.219	1.008	.314
M26	-.208	-1.002	.316
gender	.320	.970	.332
M18	-.210	-.963	.336
M49	-.212	-.926	.355
M37	-.196	-.879	.380
M43	.181	.866	.386
M27	-.156	-.789	.430
M23	-.161	-.785	.432
M48	-.130	-.663	.507
M21	-.116	-.579	.563
M14	-.097	-.495	.621
M50	-.108	-.493	.622
M44	.068	.343	.732

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M25	-.062	-.313	.754
M33	-.057	-.290	.772
M29	.053	.240	.810
estimated intelligence	.031	.136	.892
M46	-.025	-.122	.903
M8	-.022	-.082	.935
M5	-.017	-.078	.937
M34	-.017	-.070	.944
M30	-.013	-.062	.951

ADHD= Attention-deficit/hyperactivity disorder; df. = Degrees of freedom; p = uncorrected p-value; Perm. p = p-value using permutation testing; LOO-CV = Leave one participant out cross-validation method

* Nominal significant (p<.05)

** Overall regression model that is significant after multiple comparisons using the Bonferroni-Holm method p< (.05/4) or an individual regressor that remains significant after correction p < (.05/40). The thresholds are determined based on the number of independent regressions (adult ADHD, estimated intelligence, age and gender) or the number of predictors in each individual model (37 Imaging Markers, estimated intelligence, age and gender).

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Methods: Supplementary Table 4

Repetition of the logistic regression model on adult ADHD now with all 50 imaging markers included into the model. Detailed overview of the model

Supplementary Table 4: Logistic regression on adult ADHD with 50 imaging markers

<i>N=180</i>	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>Accuracy</i>	<i>p</i>
Descriptive logistic regression	130	49	34.56%	77.06%	<.001**
	<i>Cross validation</i>	-			<i>Perm. p</i>
Predictive logistic regression	LOO-CV	-		58.23%	<.011**
Individual regressors	<i>Regression coefficient</i>	<i>z-stats</i>			<i>p</i>
M19	.752	3.223			.001**
M6	.602	2.253			.024*
M32	.530	2.162			.031*
M47	-.597	-2.040			.041*
M2	.489	2.037			.042*
M38	-.439	-1.884			.060
M4	-.426	-1.837			.066
M17	.454	1.770			.077
M1	-.489	-1.700			.089
M7	.463	1.620			.105
M31	-.366	-1.612			.107

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M15	.387	1.576	.116
M13	.735	1.351	.177
M20	.299	1.312	.190
M18	-.274	-1.234	.217
M11	-.629	-1.213	.225
M36	-.279	-1.194	.232
M10	.596	1.133	.257
M3	-.263	-1.095	.274
M45	-.258	-1.086	.277
M42	-.238	-1.055	.291
M27	-.211	-.984	.325
M40	.219	.971	.332
M22	.208	.948	.343
M43	.206	.932	.351
M41	.182	.884	.376
M35	-.210	-.872	.383
M49	-.192	-.842	.400
M30	-.186	-.834	.404
M29	.151	.630	.528
M37	-.149	-.626	.531
M16	-.233	-.625	.532

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M23	-0.130	-0.579	.562
M26	-0.133	-0.560	.576
M12	-0.206	-0.520	.603
M25	-0.102	-0.491	.623
M8	.135	.489	.625
M9	-0.078	-0.439	.661
M34	-0.081	-0.367	.714
M28	-0.071	-0.304	.761
M44	.059	.273	.785
M14	-0.049	-0.227	.821
M50	-0.044	-0.185	.854
M48	-0.034	-0.172	.864
M33	-0.027	-0.127	.900
M39	.023	.104	.917
M5	.021	.082	.934
M21	.008	.039	.969
M46	-0.007	-0.033	.974
M24	.002	.013	.990

ADHD= Attention-deficit/hyperactivity disorder; df. = Degrees of freedom; p = uncorrected p-value; Perm. p = p-value using permutation testing; LOO-CV = Leave one participant out cross-validation method

*** Nominal significant (p<.05)**

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**** Overall regression model that is significant after multiple comparisons using the Bonferroni-Holm method $p < (.05/4)$ or an individual regressor that remains significant after correction $p < (.05/50)$. The thresholds are determined based on the number of independent regressions (adult ADHD, estimated intelligence, age and gender) or the number of predictors in each individual model (50 Imaging Markers).**

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Methods: Supplementary Table 5

Comparison of logistic regressions on adult ADHD with 40, 45, 50 prespecified ICA decompositions. Correlation of the top imaging markers across those models. Detailed overview of the model

Supplementary Table 5: Logistic regression on adult ADHD with 40, 45 and 50 imaging marker ICAs

Logistic regression 50 imaging markers	df. residuals	df. model	Pseudo R ²	Accuracy	p
<i>Descriptive logistic regression</i>	130	49	34.56%	77.06%	<.001**
	<i>Cross validation</i>	-	-	-	<i>Perm. p</i>
<i>Predictive logistic regression</i>	LOO-CV	-	-	58.23%	<.011**
Logistic regression 45 imaging markers	df. residuals	df. model	Pseudo R ²	Accuracy	p
<i>Descriptive logistic regression</i>	135	44	35.40%	77.01%	<.001**
	<i>Cross validation</i>	-	-	-	<i>Perm. p</i>
<i>Predictive logistic regression</i>	LOO-CV	-	-	62.68%	<.001**
Logistic regression 40 imaging markers	df. residuals	df. model	Pseudo R ²	Accuracy	p
<i>Descriptive logistic regression</i>	140	39	32.42%	78.75%	<.001**
	<i>Cross validation</i>	-	-	-	<i>Perm. p</i>
<i>Predictive logistic regression</i>	LOO-CV	-	-	60.92%	<.002**
Top imaging markers for adult ADHD with	Top imaging markers for adult ADHD with	Top imaging markers for adult ADHD with	Correlations		

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ICA model 50	ICA model 45	ICA model 40	
M19(1 ^a)	M26(1 ^a)	-	r = .955#
M19(1 ^a)	-	M23(1 ^a)	r = .970#
M6(2 ^a)	M9(2 ^a)	-	r = .725#
M6(2 ^a)	-	M7(3 ^a)	r = .975#

ADHD= Attention-deficit/hyperactivity disorder; df. = Degrees of freedom; p = uncorrected p-value; Perm. p = p-value using permutation testing; LOO-CV = Leave one participant out cross-validation method

** Significant after multiple comparisons ($p < .05/3$) for three different logistic regressions on adult ADHD with ICA model 50, 45 and 40

Multiple comparison corrected significant correlations

^a Position of marker in model on adult ADHD

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Methods: Supplementary Table 6

To inspect if the main results on adult ADHD are linked to the selection of participants, we split our sample in two parts by taking odd and even participants for both groups apart. We repeated the analyses in each of these splits for the most predictive imaging markers in the main analysis and compared the outcome.

Supplementary Table 6: Logistic regression on adult ADHD in full and split half samples, using nominal significant imaging markers from the main analysis				
Full sample	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>p</i>
Descriptive logistic regression N=180	174	5	15.14%	<.001
Split odd sample	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>p</i>
Descriptive logistic regression N=89	83	5	10.08%	.029
Split even sample	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>p</i>
Descriptive logistic regression N=91	85	5	21.67%	<.001
ADHD= Attention-deficit/hyperactivity disorder; df. = Degrees of freedom; p = uncorrected p-value;				

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Methods: Supplementary Table 7

Detailed overview of the linear regression on estimated intelligence including all imaging markers as in the logistic regression on adult ADHD presented in Supplementary Table 2. The results are depicted in Figure 2.

Supplementary Table 7: Linear regression on estimated intelligence

<i>N=180</i>	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>p</i>
<i>Descriptive logistic regression</i>	143	37	32.21%	.007**
<i>Individual regressors</i>	<i>Regression coefficient</i>	<i>t-stats</i>	<i>p</i>	
M35	.309	4.101	<.001	
M4	.225	2.904	.004	
M19	.193	2.713	.007	
M50	-.195	-2.654	.008	
M22	.120	1.660	.099	
M48	-.102	-1.447	.150	
M26	.098	1.309	.193	
M25	.092	1.286	.201	
M21	.091	1.271	.206	
M33	.086	1.207	.229	
M8	.099	1.090	.277	
M27	.075	1.059	.291	
M36	.065	.915	.362	

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M46	-.061	-.855	.394
M29	-.060	-0.830	.408
M45	.061	.806	.422
M30	-.059	-.788	.432
M43	-.055	-.777	.439
M5	.059	.773	.441
M3	.057	.751	.454
M20	.053	.750	.455
M15	.056	.731	.466
M47	-.061	-.710	.479
M1	-.057	-.647	.519
M40	.045	.601	.549
M18	.039	.541	.589
M17	.038	.530	.597
M34	.032	.446	.656
M31	-.032	-.445	.657
M49	-.032	-.416	.678
M44	.017	.235	.815
M6	-.015	-.184	.854
M37	-.011	-.148	.883

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M32	-.006	-.080	.936
M38	-.005	-.072	.943
M14	.002	.027	.978
M23	-.001	-.016	.987

df. = Degrees of freedom; p = uncorrected p-value;

* Nominal significant (p<.05)

** Overall regression model that is significant after multiple comparisons using the Bonferroni-Holm method $p < (.05/4)$ or an individual regressor that remains significant after correction $p < (.05/37)$. The thresholds are determined based on the number of independent regressions (adult ADHD, estimated intelligence, age and gender) or the number of predictors in each individual model (37 Imaging Markers), respectively.

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Methods: Supplementary Table 8

Detailed overview of the linear regression on age including all imaging markers as in the logistic regression on adult ADHD presented in Supplementary Table 2. The results are depicted in Figure 2.

Supplementary Table 8: Linear regression on age

<i>N=180</i>	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>p</i>
<i>Descriptive logistic regression</i>	143	37	78.82%	<.001**
<i>Individual regressors</i>	<i>Regression coefficient</i>	<i>t-stats</i>	<i>p</i>	
M1	-.377	-7.547	<.001	
M3	-.318	-7.359	<.001	
M8	-.228	-4.427	<.001	
M49	-.155	-3.598	<.001	
M4	-.123	-2.807	.006	
M48	-.099	-2.491	.014	
M35	-.102	-2.389	.018	
M17	-.093	-2.311	.022	
M37	-.092	-2.246	.026	
M30	.086	2.034	.044	
M43	.079	1.963	.052	
M6	-.080	-1.751	.082	
M40	.073	1.735	.085	

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M5	.073	1.695	.092
M38	-.068	-1.685	.094
M47	.082	1.677	.096
M34	-.067	-1.665	.098
M26	-.070	-1.665	.098
M20	-.062	-1.529	.129
M19	-.051	-1.273	.205
M18	.050	1.220	.225
M36	-.044	-1.108	.270
M50	-.042	-.998	.320
M22	-.036	-.882	.379
M29	-.034	-.836	.405
M44	-.028	-.687	.493
M27	.025	.632	.528
M15	-.025	-.586	.559
M21	.023	.563	.574
M33	.022	.536	.593
M32	-.020	-.475	.636
M46	.015	.364	.717
M45	-.008	-0.194	.846

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M23	.006	.159	.874
M14	-.005	-.114	.909
M31	-.004	-.100	.921
M25	<.001	.016	.987

df. = Degrees of freedom; p = uncorrected p-value;

* Nominal significant (p<.05)

** Overall regression model that is significant after multiple comparisons using the Bonferroni-Holm method $p < (.05/4)$ or an individual regressor that remains significant after correction $p < (.05/37)$. The thresholds are determined based on the number of independent regressions (adult ADHD, estimated intelligence, age and gender) or the number of predictors in each individual model (37 Imaging Markers).

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Methods: Supplementary Table 9

Detailed overview of the logistic regression on gender including all imaging markers as in the logistic regression on adult ADHD presented in Supplementary Table 2. The results are depicted in Figure 2.

Supplementary Table 9: Logistic regression on gender

<i>N=180</i>	<i>df. residuals</i>	<i>df. model</i>	<i>Pseudo R²</i>	<i>Accuracy</i>	<i>p</i>
<i>Descriptive logistic regression</i>	143	26	57.51%	90.2%	<.001**
	<i>cross validation</i>	-		<i>Accuracy</i>	<i>Perm. p</i>
<i>Predictive logistic regression</i>	LOO-CV	-		80.50%	.001**
<i>Individual regressors</i>	<i>Regression coefficient</i>	<i>z-stats</i>	<i>odds</i>	<i>p</i>	
M34	-2.120	-4.797	.120	<.001	
M3	-2.668	-4.487	.069	<.001	
M35	1.784	3.578	5.954	<.001	
M43	1.087	3.347	2.964	<.001	
M29	-1.339	-3.249	.262	.001	
M22	-1.120	-3.063	.301	.002	
M18	-1.174	-3.036	.309	.002	
M6	-1.248	-2.726	.287	.006	
M50	-.901	-2.399	.406	.016	
M14	.807	2.369	2.242	.018	

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M45	.674	2.240	1.962	.025
M17	.605	1.991	1.832	.046
M8	.863	1.893	2.371	.058
M4	.620	1.863	1.860	.063
M27	-.575	-1.777	.563	.076
M37	.489	1.545	1.630	.122
M30	-.499	-1.369	.607	.171
M47	-.573	-1.294	.564	.195
M25	.401	1.288	1.493	.198
M46	.437	1.229	1.549	.219
M21	.412	1.211	1.510	.226
M20	.347	1.199	1.415	.230
M23	.400	1.198	1.491	.231
M33	.404	1.197	1.497	.231
M49	.468	1.176	1.596	.240
M31	.393	1.108	1.482	.268
M48	.400	.976	1.491	.329
M5	-.290	-.973	.748	.330
M26	-.267	-.749	.766	.454
M36	-.223	-.639	.800	.523

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M32	-.164	-.479	.848	.632
M38	.1336	.459	1.143	.646
M19	-.149	-.425	.862	.671
M1	-.169	-.403	.845	.687
M15	.122	.370	1.130	.711
M44	.078	.253	1.081	.801
M40	.058	.179	1.060	.858

ADHD= Attention-deficit/hyperactivity disorder; df. = Degrees of freedom; p = uncorrected p-value; Perm. p = p-value using permutation testing; LOO-CV = Leave one participant out cross-validation method
 * Nominal significant (p<.05)

** Overall regression model that is significant after multiple comparisons using the Bonferroni-Holm method p< (.05/4) or an individual regressor that remains significant after correction p < (.05/40). The thresholds are determined based on the number of independent regressions (adult ADHD, estimated intelligence, age and gender) or the number of predictors in each individual model (37 Imaging Markers, estimated intelligence, age and gender).

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Supplementary Figure 1: Imaging markers are ranked based on their explained variance across modalities, meaning that a marker with a low index explains more of the variance present among the structural and diffusion modalities. Markers flanked by a red x are excluded from all statistical analyses for reasons described in supplementary table 1. Note: FA = Fractional anisotropy, MD = Mean diffusivity, MO = Tensor mode, TH = Cortical thickness, AR = Pial surface area, GM = Gray matter volume

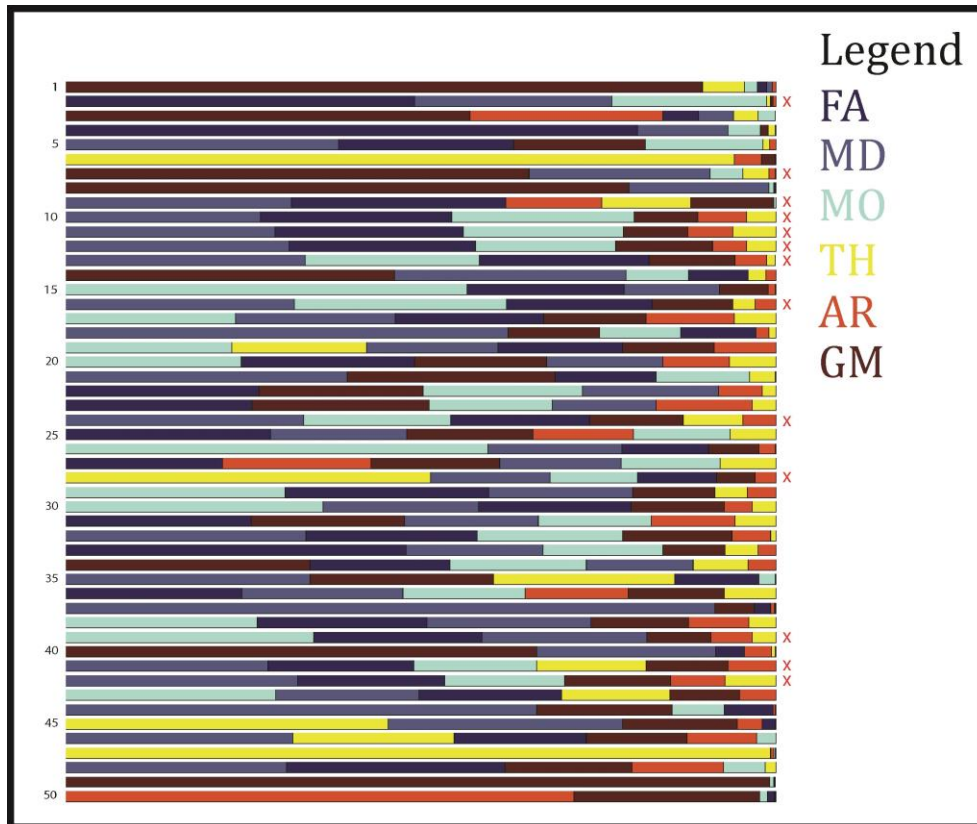
Supplementary Figure 2: Depicted are all correlations of the top imaging markers (Marker 6 and 19) contributing to the prediction of adult ADHD, with self-reported symptom scores of inattention and hyperactivity. In the first row, across the two groups in the second only for participants with ADHD in the third only for healthy controls.

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