Supplemental Material

Classification of amyotrophic lateral sclerosis by brain volume, connectivity, and network dynamics

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1 Methods

Table S1. Study overview on resting state functional connectivity studies in ALS

first author	year	ALS/HC (n)	matched for	summary findings	ROIs	analyses
Agosta	2011	26/15	age, gender	SMN	yes	seed-based
Agosta	2013	20/15	no	DMN	yes	voxel-based RSN comparisons
Bueno	2019	20/10	na	DMN	yes	ICA
Bueno	2018	20/15	no	SUBC	yes	seed-based
Chenji	2016	21/34	age	n.s.	yes	seed-based
Douaud	2011	20/15	age, gender, handness	SMN	na	tractography-derived FC
Fekete	2013	20/30	age, gender	SMN	yes	seed-based
Li	2017	20/23	age, gender	FPN	no	FC strength
Li	2018	20/35	age, gender	FPN	no	FC strength
Loewe	2016	20/38	age, gender, education	SMN	no	FC graphs
Menke	2018	20/0	na	SMN, FPN	yes	ICA
Menke	2017	24/10	age	SMN, FPN	yes	ICA
Meoded	2015	16/0	na	DMN, SMN	yes	whole-brain seed-based
Mohammadi	2009	20/20	na	DMN, SMN	yes	ICA
Lee	2017	20/46	age, gender	DMN, SMN	yes	seed-based
Jelsone-Swain	2010	20/20	age, gender	SMN	yes	seed-based
Schulthess	2017	20/56	demographically	SMN, DMN	yes	seed-based
Schmidt	2014	20/27	na	SMN	no	seed-based
Serra	2005	20/15	no	FPN	no	FC graphs
Shen	2018	20/0	na	n.s.	no	ReHo/ ReCo
Trojsi	2014	20/15	no	SMN, DMN	no	ICA
Qiu	2019	20/60	demographically	SMN	yes	seed-based
Zhang	2014	20/12	age, gender	SMN	yes	ReCo, ReHo
Zhou	2014	20/12	age, gender	SMN	no	ReCo, ReHo
Zhou	2016	20/44	age, gender	SMN	no	density FC

Legend. Red color indicates an increase, blue color indicates and decrease, black color indicates mixed findings with respect of FC features related to large-scale brain network. Please note, studies have not exclusively related their findings to large-scale brain networks; ALS = amyotrophic lateral sclerosis; DMN = default mode network; FC = functional connectivity; FPN = fronto-parietal network; ICA = independent component analysis; na = not available; HC = healthy controls; ReCo = regional coherence; ReHo = regional homogeneity; ROIs = regions of interest; SMN = sensorimotor network;

1.1 Description of rsDyn features

This section is aimed at providing the reader with additional intuition on the resting state dynamical features used for classification (please see Durstewitz, Huys, & Koppe, 2020, for an introduction into dynamical systems theory along examples from neuroscience and psychiatry). Consider a single neuron as an example – its electrical activity is determined by different ionic membrane currents and their interaction with the membrane potential. We can describe this system of currents, their gating variables, and membrane voltage through a set of differential equations (the famous Hodgkin-Huxley equations). These differential equations describe the temporal evolution of the dynamical variables, like the generation of the action potential and its propagation down the axon. Generally, by a dynamical system (DS) we mean such a system that evolves in time and can be described through a set of equations of motion, and essentially any physical, biological, or psychological system can be packed into this form. A central concept in DS theory is that of a state space which is the space spanned by all the system's dynamical variables (all the ion channel gating and membrane potential variables in the example above). The evolution of the system in time is given by a trajectory in this state space, and is governed by the so-called flow field, which specifies the temporal derivatives at each point in time (i.e., in which direction and with which velocity the system will continue to move). All DS share a couple of general phenomena, like for instance attractor states – the resting potential of a cell, e.g., is a fixed-point attractor, i.e. a point in state space toward which the system will always returned from some neighborhood if perturbed (e.g., by current injection). In our case, the relevant DS variables are the latent states $\mathbf{z}$ which describe the brain dynamics underlying the observed time series of BOLD measurements (cf. section 2.3). In our work we tried to capture relevant properties of the state space and its flow field, as reconstructed by our PLRNN approach, through a set of features that went into the classifiers.

Details on the exact extraction procedure for these features may be found on GitHub (https://github.com/JanineT-oss/ALS_PLRNN_classification). The generative dynamical system equation of our state space model (eqn. (1), main manuscript) provides us with a set of subject-specific parameters that summarize and quantify the resting state dynamics of each individual. For one, the equation enables the analytical assessment of fixed points (which, formally, satisfy the condition $\mathbf{z}^* = f(\mathbf{z}^*) = \mathbf{A}\mathbf{z}^* + \mathbf{W}\varphi(\mathbf{z}^*) + \mathbf{h}$, i.e., states $\mathbf{z}^*$ at which the system remains when put there) and k-cycles (which are oscillatory behaviors with a period given by k). Fixed points and cycles are important dynamical phenomena, and both of them can be 'attracting' (meaning state space trajectories are drawn toward them), 'repelling' (meaning trajectories are pushed away from them), or in between (so-called 'saddles', toward which states

converge along some and diverge along other directions in state space). Attracting states (whether fixed points or cycles, there are also 'chaotic' attractors) have been associated with the maintenance of distinct mental representations such as memories or decisions (e.g., Albantakis & Deco, 2009; Durstewitz, Seamans, & Sejnowski, 2000; Wang, 2001). Activity around unstable fixed points or cycles, in contrast, diverges from one or more directions, which may give rise to more complex phenomenon (see Durstewitz et al., 2020; Rabinovich, Huerta, Varona, & Afraimovich, 2008). Quantifying the number of stable and unstable fixed points and *k*-cycles of a system (as reflected in FD1, FD2, and FD 10) thus provides some information on its overall behavior in state space.

Besides the assessment of the location and type of a fixed point, we can use eqn. (1) to further quantify more precisely the behavior of the system around these points. The eigenvalues of the PLRNN's transition matrices around fixed or cyclic points (as used for FD3-4) provides additional information on oscillatory behavior and the speed of con- or divergence. For instance, while the imaginary parts of the eigenvalues are indicative of spiral behavior around these points, the deviation of the maximum absolute eigenvalue from 1 tells us how close a system is to specific types of bifurcation (cf. Durstewitz, 2017). Bifurcations are sudden qualitative changes in the system dynamics which occur as one or more of the system's parameters are gradually changed (e.g., like the transition of a neuron's membrane potential from a steady resting state to repetitive spiking as the amount of injected current is gradually increased). At the level of cognitive function, they may for instance account for sudden onsets of symptoms in neurological and mental disorders (such as the sudden onset of an epileptic seizure; Jirsa, Stacey, Quilichini, Ivanov, & Bernard, 2014; see also Durstewitz et al., 2020).

Other statistics inform us about the velocity along trajectories in state space, like the distance travelled per unit time, or about the spread of states across regions of state space, like the variance over time in these states. Since ultimately all the system's dynamical features are encoded in its parameters, albeit often indirectly and hidden, analyzing PLRNN parameters directly may also give some insights (e.g., features FD5-13). While the bias parameters **h** (eqn. (1)) determines the mean activity of the system, other properties of the transition matrix rather than its eigenvalue spectrum may provide additional information on several properties: For instance, the variance of parameters in a recurrent neural network's transition matrix is an important control parameter that determines how orderly or chaotic such a network behaves (Bertschinger & Natschläger, 2004). This, in turn, has implications for cognition: In a regime close to the edge of chaos, recurrent neural networks have been found to perform many computations optimally. Note that the PLRNN's transition matrix **W** represents the

connectivity or coupling between different state variables. By averaging over these values, or the *absolute* values of **W**, we characterize how balanced (around 0) or biased the connectivity is, as well as the average connection strengths, respectively. In addition to evaluating the entire transition matrix, we also included features assessed separately on the regularized and non-regularized parts of the transition matrix. This was done to be able to distinguish between dynamics relating to slower (regularized) vs. faster (non-regularized) time scales (please see Schmidt, Koppe, Beutelspacher, & Durstewitz, 2020 for details).

1.2 Controlling for age. We classified groups based on an age median split to check whether age, despite matching the groups by age, captures important information in classifying group membership. In detail, the classification was performed by computing the age median and classifying individuals based on their current age as ALS (i.e., age > age median) or HC (i.e., age ≤ age median). The estimation of the out-of-sample prediction error (PE) was performed following the 5-fold CV protocol (cf. 2.4), whereby the age median was inferred for each training set and individuals of the test set were classified accordingly.

The age classifier revealed a mean balanced accuracy of 60.85 %, a sensitivity of 58.51 %, and a specificity of 63.20% (see Figure S1), revealing that age captures discriminatory information in classifying group membership. Critically, with respect to this finding, classification performance of the neuroimaging classifiers could hence be partly driven by age instead of the neuroimaging features itself. We thus additionally removed linear effects of age from all features before classification.

2 Results

2.1 Individual feature classification

To examine the classification performance of single features (compared with multivariate features), we additionally implemented single feature classifiers (all features N = 169; VOL: N = 19; rsFC: N = 132; rsDyn: N = 18).

This was achieved by training an RF classifier on each feature individually (cf. for the exact protocol see section 2.4). The estimation of the out-of-sample PE was performed following the 5-fold CV protocol. This procedure was repeated for each of the 169 features. Results are presented in Table S6.

2.2 Validating classifiers on an independent sample: ALS mimics

We applied the trained classifiers on an additional independent test set comprising ten ALS mimics. These were individuals suffering from other conditions than ALS but sharing symptomatology. For all these individuals, ALS was a suspected differential diagnosis at the time of MRI acquisition. However, they suffered from other conditions as evaluated through regular follow-up as follows: Parkinson's disease (n=1), Polyneuropathy (n=1 paraneoplastic, n=1 diabetic Mononeuritis multiplex), Facioscapulohumeral Muscular Dystrophy (n=1), Kennedy's disease/bulbospinal muscular atrophy (n=1), limb-girdle muscular dystrophy (n=1), Adrenomyeloneuropathy (n=1), Cervical spinal stenosis (n=2), Benign fasciculations (n=1). Subjects were preprocessed and features extracted in agreement with the procedure of the ALS and healthy samples (cf. section 2.3). The classifiers trained on ALS and healthy control subjects were then applied on these ALS mimics (cf. section 2.4).

For the unimodal classifiers, classification specificities of 64.80%, 66.11%, and 59.60% were obtained for brain volume, resting state functional connectivity, and resting state dynamics, respectively. Feature set combinations revealed specificities ranging between 64.03% – 68.06%, with the combination of all three feature sets outperforming all other feature sets. We therefore concluded that the RF classifiers trained on ALS and healthy control individuals did learn ALS-specific discriminatory information.

Table S2. Brain Volumetrics in Healthy Controls as compared with Individuals with ALS.

		ALS		HC		STATS					
	HS	**mean**	**SD**	**mean**	**SD**	**T-value**	**dof**	***p***	***padj***		**dcohen**
global brain volume											
GM	na	-3.254	67.50	14.517	57.43	1.68	153	0.095	>.1		0.28
GM normalized	na	-0.004	0.03	0.007	0.03	2.29	152	0.023	>.1		0.01
WM	na	-3.565	62.40	13.097	50.30	1.73	153	0.085	>.1		0.29
WM normalized	na	-0.002	0.03	0.007	0.02	2.44	152	0.016	>.1		0.05
CSF	na	12.243	74.40	-17.870	69.18	2.51	152	0.013	0.093		0.42
CSF normalized	na	0.007	0.03	-0.014	0.03	3.69	151	<0.001	0.002	**	0.61
TIV	na	7.667	142.96	9.745	136.04	0.09	153	>.1	>.1		0.02
regional^ brain volume											
SMN											
pre/postcentral cortex	L	-5.68177E-05	0.0002675	2.0492E-06	0.0002126	1.43	152	>.1	>.1		0.38
pre/postcentral cortex	R	-2.30011E-05	0.000285	5.35562E-05	0.0002408	1.72	152	0.088	>.1		0.38
thalamus	L	2.6334E-08	1.706E-06	1.71153E-07	1.554E-06	0.53	153	>.1	>.1		0.12
thalamus	R	1.11072E-07	1.361E-06	-2.57097E-08	9.329E-07	0.68	153	>.1	>.1		0.13
cerebellum	L/R	8.25187E-06	0.0004322	5.01376E-05	0.0004268	0.59	152	>.1	>.1		0.11
SMA	L/R	-3.01813E-06	4.292E-05	9.31565E-06	4.227E-05	1.75	153	0.083	0.992		0.30
DMN											
mPFC	L/R	-0.000117822	0.0011671	0.000375185	0.0009672	2.72	153	0.007	0.087	(*)	0.44
PCC	L/R	-7.25904E-06	0.0003923	5.20552E-05	0.0003397	0.96	152	>.1	>.1		0.19
FPN											
SPC	L	-0.00016566	0.0004373	-9.69245E-05	0.0003236	1.04	153	>.1	>.1		0.30
IPC	R	-2.6436E-05	0.0003529	5.58808E-05	0.0003144	1.46	151	>.1	>.1		0.19
SFG	L	-6.59435E-05	0.0003433	-2.64504E-07	0.0001745	1.30	147	>.1	>.1		0.22
SFG	R	-6.46579E-06	0.0004878	6.63666E-05	0.0003506	0.99	152	>.1	>.1		0.17

$^{**}p/p_{adj}<0.01$; $^{(*)}p/p_{adj}<0.1$; ^normalized

Legend: adj = Bonferroni-adjusted threshold; ALS = amyotrophic lateral sclerosis; CSF = cerebrospinal fluid; DMN = default mode network; d_{Cohen} = effect sizes calculated according to Cohen's d for unequal sample sizes; *FPN = fronto-parietal network; GM = gray matter; HC = healthy controls; IPC = inferior parietal cortex; HS = hemisphere; L = left; mPFC = medial prefrontal cortex; na = not applicable; PCC = posterior cingulate cortex; p = p-value; R = right; SD = standard deviation; SFG = superior frontal gyrus; SMA = supplementary motor area; SMN = sensorimotor network; SPC = superior parietal gyrus; TIV = transcranial volume; WM = white matter*

Table S3. Resting State Functional Connectivity between ROIs in Healthy Controls as compared with Individuals with ALS

	PCC b				mPFC b				IPC r	SFC l	SFC r	SPC l	Cereb b	PrePost l	PrePost r	SMA b	Thal l
	T	dof	p_{adj}	d_c	T	dof	p_{adj}	d_c	p_{adj}	p_{adj}	p_{adj}	p_{adj}	p_{adj}	p_{adj}	p_{adj}	p_{adj}	p_{adj}
PCC b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
mPFC b	4.58	146	.001	0.77	-	-	-	-	-	-	-	-	-	-	-	-	-
IPC r	5.24	147	<.001	0.88			>.1		-	-	-	-	-	-	-	-	-
SFG l	5.76	147	<.001	0.96			>.1		>.1	-	-	-	-	-	-	-	-
SFG r	5.69	146	<.001	0.97	3.83	146	.024	0.59	>.1	>.1	-	-	-	-	-	-	-
SPC l	4.86	144	<.001	0.82			>.1		>.1	>.1	>.1	-	-	-	-	-	-
Cereb b	5.37	148	<.001	0.9			>.1		>.1	>.1	>.1	>.1	-	-	-	-	-
PrePost l	5.22	147	<.001	0.89			>.1		>.1	>.1	>.1	>.1	>.1	-	-	-	-
PrePost r	5.51	147	<.001	0.93			>.1		>.1	>.1	>.1	>.1	>.1	>.1	-	-	-
SMA b	5.54	147	<.001	0.93			>.1		>.1	>.1	>.1	>.1	>.1	>.1	>.1	-	-
Thal l	5.54	147	<.001	0.93			>.1		>.1	>.1	>.1	>.1	>.1	>.1	>.1	>.1	-
Thal r	5.54	147	<.001	0.93			>.1		>.1	>.1	>.1	>.1	>.1	>.1	>.1	>.1	>.1

Legend. red color indicates the default mode network; green color indicates the fronto-parietal network; blue color indicates the sensorimotor network; adj = Bonferroni-adjusted threshold; ALS = amyotrophic lateral sclerosis; b = bilateral; Cereb = cerebellum; d_C = effect sizes calculated according to Cohen's d for unequal sample sizes; dof = degrees of freedom; *IPC = inferior parietal cortex; l = left; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; p = p-value; PrePost = precentral/ postcentral cortex; r = right; SFG = superior frontal gyrus; SMA = supplementary motor area; SPC = superior parietal gyrus; T = T-value; Thal = thalamus*

Table S4. Brain Dynamics in Healthy Controls as compared with Individuals with ALS.

	ALS		HC		STATS					
	mean	**SD**	**mean**	**SD**	**T-value**	**dof**	***p***	p_{adj}		d_{cohen}
FD 1	-0.117	1.471	-0.280	1.328	0.678	143	>.1	>.1		0.11
FD 2	-0.047	1.517	-0.401	1.327	1.440	143	>.1	>.1		0.24
FD 3	0.001	0.195	-0.014	0.206	0.442	147	>.1	>.1		0.08
FD 4	0.018	0.061	0.024	0.068	-0.490	139	>.1	>.1		0.09
FD 5	-0.093	0.174	-0.060	0.193	-1.034	138	>.1	>.1		0.18
FD 6	-0.001	0.019	-0.004	0.016	1.011	144	>.1	>.1		0.17
FD 7	-0.186	0.353	-0.121	0.382	-1.027	138	>.1	>.1		0.18
FD 8	-0.024	0.059	0.001	0.086	-2.030	140	0.044	>.1		0.35
FD 9	-0.373	1.554	0.021	2.127	-1.294	144	>.1	>.1		0.33
FD 10	-1.078	1.120	-1.372	1.019	1.546	136	>.1	>.1		0.27
FD 11	0.010	0.130	-0.001	0.138	0.485	146	>.1	>.1		0.08
FD 12	-0.059	0.851	0.076	0.924	-0.885	140	>.1	>.1		0.15
FD 13	-0.029	0.269	0.030	0.281	-1.288	147	>.1	>.1		0.22
FD 14	-1.121	2.789	-0.395	4.521	-1.181	139	>.1	>.1		0.20
FD 15	-1.023	0.763	-1.235	0.544	1.721	134	0.088	>.1		0.31
FD 16	-0.003	0.040	0.001	0.041	-0.546	146	>.1	>.1		0.09
FD 17	0.026	0.080	0.053	0.053	-2.033	131	0.044	>.1		0.37
FD 18	-0.001	0.006	-0.004	0.004	3.613	138	<0.001	0.008	**	0.63

***p/p_{adj}<0.01*

Legend. adj = Bonferroni-adjusted threshold; ALS = amyotrophic lateral sclerosis; d_{Cohen} = effect sizes calculated according to Cohen's d for unequal sample sizes; dof = degrees of freedom; *FD = feature dynamics; HC = healthy controls; SD = standard deviation; p = p-value*

Table S5. Classification performance of all RF classifiers classifying ALS mimics.

Feature set	specificity	
	mean	SEM
VOL	64.80	2.47
rsFC	66.11	1.10
rsDyn	59.60	2.37
VOL+rsFC	67.94	6.36
VOL+rsDyn	64.29	2.96
rsFC+rsDyn	64.03	4.57
VOL+rsFC+rsDyn	**68.06**	3.09

Legend. bold = highest performance; rsFC = resting state functional connectivity; rsDyn = resting state dynamics; SEM = standard error of the mean; VOL = brain volume

Table S6. Classification performance of single RF classifiers on single features

Feature	accuracy		sensitivity		specificity	
	mean	SEM	mean	SEM	mean	SEM
VOL GM	49.71	2.57	52.23	1.69	47.2	5.07
VOL WM	54.12	1.61	51.17	1.53	57.07	2.21
VOL CSF	49.84	1.24	49.28	1.59	50.4	2.75
VOL TIV	48.42	1.12	48.3	2.71	48.53	2.69
VOL GM ^	43.59	1.11	42.64	2.04	44.53	2.55
VOL WM ^	57.04	1.57	53.81	1.72	60.27	4.78
VOL CSF ^	51.42	1.1	53.51	0.88	49.33	2.23
VOL DMN PCC b ^	50.19	1.16	48.91	1.14	51.47	3.17
VOL DMN mPFC b ^	53.24	0.94	52.08	1.54	54.4	1.36
VOL FPN IPC r ^	53.45	1.71	46.64	2.78	60.27	3.11
VOL FPN SFG r ^	48.73	1.54	47.32	2.62	50.13	2
VOL FPN SFG l ^	54.78	1.59	56.75	2.81	52.8	2.33
VOL FPN SPC l ^	48.67	1.14	47.47	2.24	49.87	2.48
VOL SMN Cereb b ^	48.66	1.24	44.53	1.73	52.8	1.72
VOL SMN PrePostC l ^	52.68	1	49.36	2.89	56	2.42
VOL SMN PrePostC r ^	42.76	0.82	44.98	2.18	40.53	2.25
VOL SMN SMA b ^	47.49	0.97	46.72	1.81	48.27	1.29
VOL SMN Thal l ^	50.64	0.51	52.75	1.25	48.53	1.5
VOL SMN Thal r ^	59.19	1.05	57.58	1.75	60.8	2.41
FD 1	51.45	0.96	51.75	1.08	51.14	2.28
FD 2	54.03	1.65	50.92	1.31	57.14	3.29
FD 3	53.86	1.64	52.58	0.87	55.14	3.31
FD 4	51.39	0.87	48.5	1.87	54.29	3.1
FD 5	54.33	1.59	56.08	2.09	52.57	3.74
FD 6	52.62	0.42	52.67	1.86	52.57	2.28
FD 7	56.45	1.46	53.75	1.43	59.14	2.95
FD 8	49.04	0.87	49.5	1.54	48.57	1.01
FD 9	58.89	1.04	54.92	1.34	62.86	1.81
FD 10	48.52	1.34	49.33	2.85	47.71	4.06
FD 11	44.63	1.43	47.25	1.57	42	3.18
FD 12	47.02	1.51	44.33	2.46	49.71	3.18
FD 13	52.71	0.43	52	1.95	53.43	1.84
FD 14	53.46	0.72	52.92	2.21	54	1.05
FD 15	47.39	1.2	44.5	1.98	50.29	3.08
FD 16	51.38	1.88	54.75	1.4	48	2.42
FD 17	48.25	0.68	46.5	1.61	50	1.43
FD 18	52.44	1.72	59.17	1.3	45.71	2.93
FC DMN PCC b by DMN mPFC b	61.36	1.73	59	2.25	63.71	3.02
FC DMN PCC b by FPN IPC r	57.04	0.97	57.5	2.12	56.57	1.32
FC DMN PCC b by FPN SFG r	65.57	1.07	65.42	0.23	65.71	2.07

FC DMN PCC b by FPN SFG l	61.5	0.81	63	2.25	60	3.35
FC DMN PCC b by FPN SPC l	57.68	1.14	59.08	2.47	56.29	0.35
FC DMN PCC b by SMN Cereb b	59.4	1.8	61.08	2.06	57.71	2
FC DMN PCC b by SMN PrePostC l	65.08	1.08	63.58	1.31	66.57	1.16
FC DMN PCC b by SMN PrePostC r	58.26	0.6	59.08	1.96	57.43	2.23
FC DMN PCC b by SMN SMA b	60.24	1.02	61.92	3.73	58.57	4.21
FC DMN PCC b by SMN Thal l	60.46	0.5	61.5	3.17	59.43	3.05
FC DMN PCC b by SMN Thal r	61.02	1.29	62.33	3.53	59.71	2.53
FC DMN mPFC b by DMN PCC b	59.74	1.47	56.33	1.99	63.14	2.19
FC DMN mPFC b by FPN IPC r	47.73	1.42	43.17	2.62	52.29	2.77
FC DMN mPFC b by FPN SFG r	46.45	1.12	46.33	0.93	46.57	1.84
FC DMN mPFC b by FPN SFG l	50.6	1.75	46.33	3.03	54.86	1.67
FC DMN mPFC b by FPN SPC l	51.95	1.14	53.33	3.83	50.57	2.73
FC DMN mPFC b by SMN Cereb b	54.4	2.05	51.08	2.14	57.71	2.81
FC DMN mPFC b by SMN PrePostC l	48.77	2.42	49.83	2.78	47.71	2.95
FC DMN mPFC b by SMN PrePostC r	55.43	0.82	54	1.1	56.86	1.94
FC DMN mPFC b by SMN SMA b	51.51	1.65	52.17	1.56	50.86	3.05
FC DMN mPFC b by SMN Thal l	51.86	1.62	54.58	2.62	49.14	5.04
FC DMN mPFC b by SMN Thal r	50.99	1.29	52.83	2.03	49.14	3.8
FC FPN IPC r by DMN PCC b	53.65	2.2	56.17	1.56	51.14	3.95
FC FPN IPC r by DMN mPFC b	53.06	1.57	57.83	2.76	48.29	1.23
FC FPN IPC r by FPN SFG r	53.16	1.33	51.75	2.1	54.57	2.41
FC FPN IPC r by FPN SFG l	53.62	1.2	54.67	2.03	52.57	2.23
FC FPN IPC r by FPN SPC l	45.3	1.16	45.17	2.12	45.43	3.33
FC FPN IPC r by SMN Cereb b	49.21	1.02	51	0.95	47.43	2.36
FC FPN IPC r by SMN PrePostC l	46.71	1.22	45.42	1.06	48	2.81
FC FPN IPC r by SMN PrePostC r	44.02	1.74	44.33	2.85	43.71	3.69
FC FPN IPC r by SMN SMA b	44.42	1.06	44.83	1.59	44	2.84
FC FPN IPC r by SMN Thal l	45.89	1.23	47.5	3.18	44.29	2.26
FC FPN IPC r by SMN Thal r	43.88	1.4	42.33	1.56	45.43	3.08
FC FPN SFG r by DMN PCC b	61.07	1.05	58.42	2	63.71	3.25
FC FPN SFG r by DMN mPFC b	43.54	0.72	47.08	2.58	40	2.02
FC FPN SFG r by FPN IPC r	57.92	1.21	57.83	3.45	58	2.05
FC FPN SFG r by FPN SFG l	44.83	1.91	47.67	2.16	42	3.63
FC FPN SFG r by FPN SPC l	44.39	1.94	49.92	1.92	38.86	3.36
FC FPN SFG r by SMN Cereb b	51.28	0.99	55.42	2.25	47.14	2.02
FC FPN SFG r by SMN PrePostC l	46.95	0.9	45.33	1.46	48.57	2.75
FC FPN SFG r by SMN PrePostC r	46.42	1.09	47.42	2.08	45.43	1.46
FC FPN SFG r by SMN SMA b	49.61	1.41	49.5	2.13	49.71	2.23
FC FPN SFG r by SMN Thal l	48.43	2.34	50.58	2.44	46.29	3.98
FC FPN SFG r by SMN Thal r	52.83	1.7	53.67	2.46	52	3.31
FC FPN SFG l by DMN PCC b	61.13	1.86	56.83	2.4	65.43	4.3
FC FPN SFG l by DMN mPFC b	52.69	3.12	51.67	1.6	53.71	5.65
FC FPN SFG l by FPN IPC r	48.42	1.7	53.42	3.4	43.43	4.03

FC FPN SFG l by FPN SFG r	46.07	2.17	44.42	1.62	47.71	4.49
FC FPN SFG l by FPN SPC l	55.49	1.91	55.83	1.45	55.14	3.57
FC FPN SFG l by SMN Cereb b	51.71	0.76	51.42	2.38	52	3.28
FC FPN SFG l by SMN PrePostC l	44.05	1.32	44.67	1.98	43.43	1.32
FC FPN SFG l by SMN PrePostC r	49.17	1.8	46.92	2.01	51.43	3.67
FC FPN SFG l by SMN SMA b	42.88	0.7	43.75	2.14	42	1.47
FC FPN SFG l by SMN Thal l	50.22	0.71	49.58	0.9	50.86	1.67
FC FPN SFG l by SMN Thal r	47.3	0.8	45.75	1.22	48.86	1.53
FC FPN SPC l by DMN PCC b	49.72	1.56	50.58	1.43	48.86	1.71
FC FPN SPC l by DMN mPFC b	49.48	1.57	49.25	2.02	49.71	2.69
FC FPN SPC l by FPN IPC r	53.21	2.45	54.42	1.81	52	3.8
FC FPN SPC l by FPN SFG r	50.15	2.24	46.58	1.73	53.71	3.25
FC FPN SPC l by FPN SFG l	51.4	0.97	49.08	1.91	53.71	0.73
FC FPN SPC l by SMN Cereb b	47.73	1.07	51.17	2.97	44.29	4.33
FC FPN SPC l by SMN PrePostC l	53.09	2.01	52.75	3.3	53.43	1.47
FC FPN SPC l by SMN PrePostC r	52.17	0.58	52.33	1.06	52	1.47
FC FPN SPC l by SMN SMA b	49.81	1.46	51.33	1.42	48.29	2.61
FC FPN SPC l by SMN Thal l	46.83	1.07	51.08	1.97	42.57	0.95
FC FPN SPC l by SMN Thal r	49.54	0.73	53.08	2.1	46	2.32
FC SMN Cereb b by DMN PCC b	56.26	0.51	57.08	0.81	55.43	1.05
FC SMN Cereb b by DMN mPFC b	57.65	2.28	54.17	2.12	61.14	2.98
FC SMN Cereb b by FPN IPC r	50.38	1.83	51.33	1.59	49.43	3.63
FC SMN Cereb b by FPN SFG r	61	1.37	58	1.42	64	1.53
FC SMN Cereb b by FPN SFG l	46.38	1.9	41.33	2.45	51.43	1.75
FC SMN Cereb b by FPN SPC l	46.09	1.6	46.75	2.58	45.43	1.65
FC SMN Cereb b by SMN PrePostC l	51.48	2.05	52.67	3.07	50.29	3.63
FC SMN Cereb b by SMN PrePostC r	49.51	2.09	46.17	2.02	52.86	5.05
FC SMN Cereb b by SMN SMA b	52.81	1.29	55.33	1.1	50.29	2.53
FC SMN Cereb b by SMN Thal l	54.64	1.05	53	1.46	56.29	1.67
FC SMN Cereb b by SMN Thal r	55.78	1.57	54.42	1.74	57.14	2.75
FC SMN PrePostC l by DMN PCC b	59.06	1.37	57.83	2.08	60.29	3.68
FC SMN PrePostC l by DMN mPFC b	49.33	1.04	52.67	1.17	46	2.19
FC SMN PrePostC l by FPN IPC r	48.32	0.76	46.92	2.95	49.71	3.24
FC SMN PrePostC l by FPN SFG r	43.4	1.05	43.67	1.4	43.14	2.32
FC SMN PrePostC l by FPN SFG l	49.38	1.3	47.33	1.87	51.43	2.35
FC SMN PrePostC l by FPN SPC l	55.69	0.88	51.67	1.61	59.71	2.32
FC SMN PrePostC l by SMN Cereb b	55.2	0.78	55.83	2.64	54.57	3.48
FC SMN PrePostC l by SMN PrePostC r	47.74	1.26	48.33	2.7	47.14	4.4
FC SMN PrePostC l by SMN SMA b	53.32	1.26	53.5	1.9	53.14	2.32
FC SMN PrePostC l by SMN Thal l	56.8	0.94	56.75	1.87	56.86	1.65
FC SMN PrePostC l by SMN Thal r	52.91	1.65	53.25	1.96	52.57	2.49
FC SMN PrePostC r by DMN PCC b	57.98	1.41	56.25	3.06	59.71	2.28
FC SMN PrePostC r by DMN mPFC b	55.65	1.2	52.17	1.45	59.14	2.98
FC SMN PrePostC r by FPN IPC r	56.23	2.03	54.75	2.49	57.71	2.77

FC SMN PrePostC r by FPN SFG r	43.53	1.21	43.92	3.33	43.14	2.09
FC SMN PrePostC r by FPN SFG l	48.63	1.32	43.83	3.41	53.43	3.12
FC SMN PrePostC r by FPN SPC l	49.11	1.92	51.08	2.41	47.14	2.52
FC SMN PrePostC r by SMN Cereb b	46.3	1.9	51.75	2.79	40.86	3.02
FC SMN PrePostC r by SMN PrePostC l	51.12	0.44	49.67	1.27	52.57	1.59
FC SMN PrePostC r by SMN SMA b	48.11	0.54	51.08	1.08	45.14	1.47
FC SMN PrePostC r by SMN Thal l	51.83	1.22	53.08	1.61	50.57	3.46
FC SMN PrePostC r by SMN Thal r	50.48	0.92	53.25	2.2	47.71	1.4
FC SMN SMA b by DMN PCC b	54.84	1.27	52.25	2.21	57.43	2.61
FC SMN SMA b by DMN mPFC b	39.42	1.6	39.42	1.94	39.43	2.29
FC SMN SMA b by FPN IPC r	54.07	1.31	54.42	2.18	53.71	4.3
FC SMN SMA b by FPN SFG r	53.48	1.07	49.25	2.01	57.71	2.62
FC SMN SMA b by FPN SFG l	59.8	0.95	56.75	1.34	62.86	2.89
FC SMN SMA b by FPN SPC l	55.17	1.85	54.92	1.64	55.43	3.01
FC SMN SMA b by SMN Cereb b	52.66	1.05	52.75	2.34	52.57	2.36
FC SMN SMA b by SMN PrePostC l	53.39	1.42	53.92	1.97	52.86	2.67
FC SMN SMA b by SMN PrePostC r	44.01	1.01	47.17	2.75	40.86	1.07
FC SMN SMA b by SMN Thal l	51.29	1.22	52.58	1.91	50	3.13
FC SMN SMA b by SMN Thal r	45.57	1.35	46	1.16	45.14	2.66
FC SMN Thal l by DMN PCC b	54.36	1.35	51.58	1.42	57.14	2.71
FC SMN Thal l by DMN mPFC b	42.93	1.53	41	0.7	44.86	2.73
FC SMN Thal l by FPN IPC r	54.52	1.37	55.33	2.36	53.71	4.39
FC SMN Thal l by FPN SFG r	55.36	1.1	51	1.42	59.71	2.19
FC SMN Thal l by FPN SFG l	60.54	0.9	58.5	0.92	62.57	1.39
FC SMN Thal l by FPN SPC l	57.21	2.09	56.42	2.86	58	3.15
FC SMN Thal l by SMN Cereb b	49.55	1.49	50.25	2.54	48.86	2.41
FC SMN Thal l by SMN PrePostC l	53.59	2.05	55.75	1.1	51.43	3.7
FC SMN Thal l by SMN PrePostC r	47.29	0.72	46	2.91	48.57	2.78
FC SMN Thal l by SMN SMA b	48.95	1.57	54.75	1.3	43.14	2.09
FC SMN Thal l by SMN Thal r	56.2	2.16	55.83	2.16	56.57	2.42
FC SMN Thal r by DMN PCC b	55.08	1	53.58	1.67	56.57	2.5
FC SMN Thal r by DMN mPFC b	44.82	1.46	45.92	1.03	43.71	2.58
FC SMN Thal r by FPN IPC r	53.27	1.35	54.83	1.67	51.71	3.97
FC SMN Thal r by FPN SFG r	55.21	1.29	49	1.54	61.43	2.56
FC SMN Thal r by FPN SFG l	57.07	1.09	54.42	2.76	59.71	1.94
FC SMN Thal r by FPN SPC l	57.94	2.25	56.17	2.34	59.71	3.39
FC SMN Thal r by SMN Cereb b	53.86	1.45	50.58	2.18	57.14	1.2
FC SMN Thal r by SMN PrePostC l	52.43	1.3	56	1.56	48.86	3.42
FC SMN Thal r by SMN PrePostC r	43.95	2.24	48.75	2.1	39.14	2.98
FC SMN Thal r by SMN SMA b	49.19	0.49	46.67	1.03	51.71	1.59
FC SMN Thal r by SMN Thal l	55.39	1.66	60.5	0.93	50.29	3.79

Legend. ^ = normalized; b = bilateral; Cereb = cerebellum; DMN = default mode network; FC = functional connectivity; FD = feature dynamics; FPN = fronto-parietal network; GM = gray matter; IPC = inferior parietal cortex; l = left; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; PrePostC = precentral/ postcentral cortex; r = right; SEM = standard error of the mean; SFG = superior frontal gyrus; SMA =

supplementary motor area; SMN = sensory motor network; SPC = superior parietal gyrus; Thal = thalamus; TIV = transcranial volume; VOL = brain volume; WM = white matter

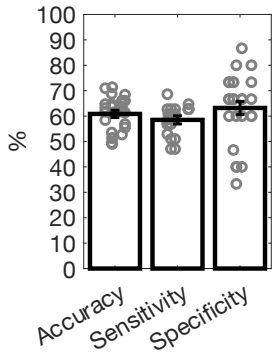

Figure S1. Years of age classifier. Mean and standard error of the mean of the classification performance of years of age.

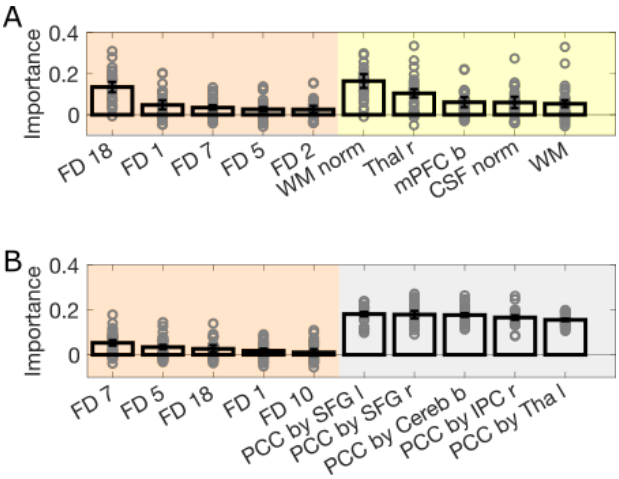

Figure S2. Random forest multimodal classifiers. The mean and standard error of the mean of feature importance scores of bimodal classifiers: A. rsDyn and VOL. B. rsDyn and rsFC.

Legend. b = bilateral; Cereb = cerebellum; CSF = cerebrospinal fluid; FD = feature dynamics; l = left; IPC = inferior parietal cortex; mPFC = medial prefrontal cortex; norm = normalized; PCC = posterior cingulate cortex; r = right; SFG = superior frontal gyrus; SPC = superior parietal gyrus; Thal = thalamus; WM = white matter

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