Supplementary Materials

Fig. S1. Schematic of subject selection. We searched the UCSF database and identified 17 preclinical *GRN* carriers, all of whom had an MRI scan. A subset of 15 of these carriers also had a tf-fMRI scan.

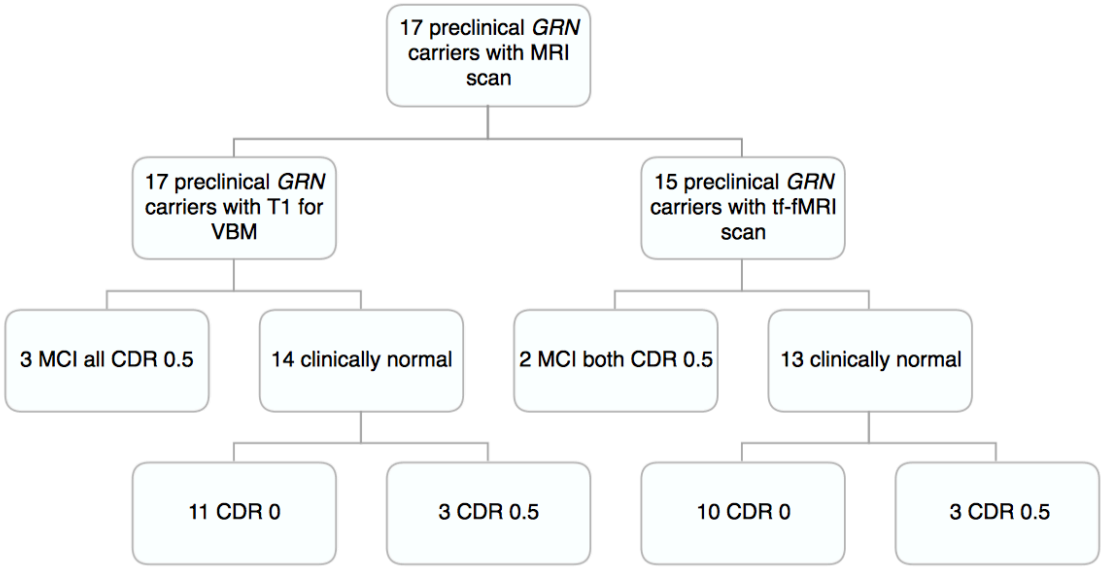

Fig. S2. Asymmetry analysis schematic. To compare connectivity symmetry, we took the left- and right-seeded thresholded maps from the *GRN* > HC comparison (Fig. 2), binarized the maps, then combined the maps into a union map of regions (green map). We then created the mirror image of this combined map (fuchsia map) and created a union map of all regions in the combined map and its mirror image (yellow map). We split the yellow map into left- (blue) and right- (red) sided regions within which mean connectivity w-scores were calculated for each ICN for each preclinical *GRN* subject.

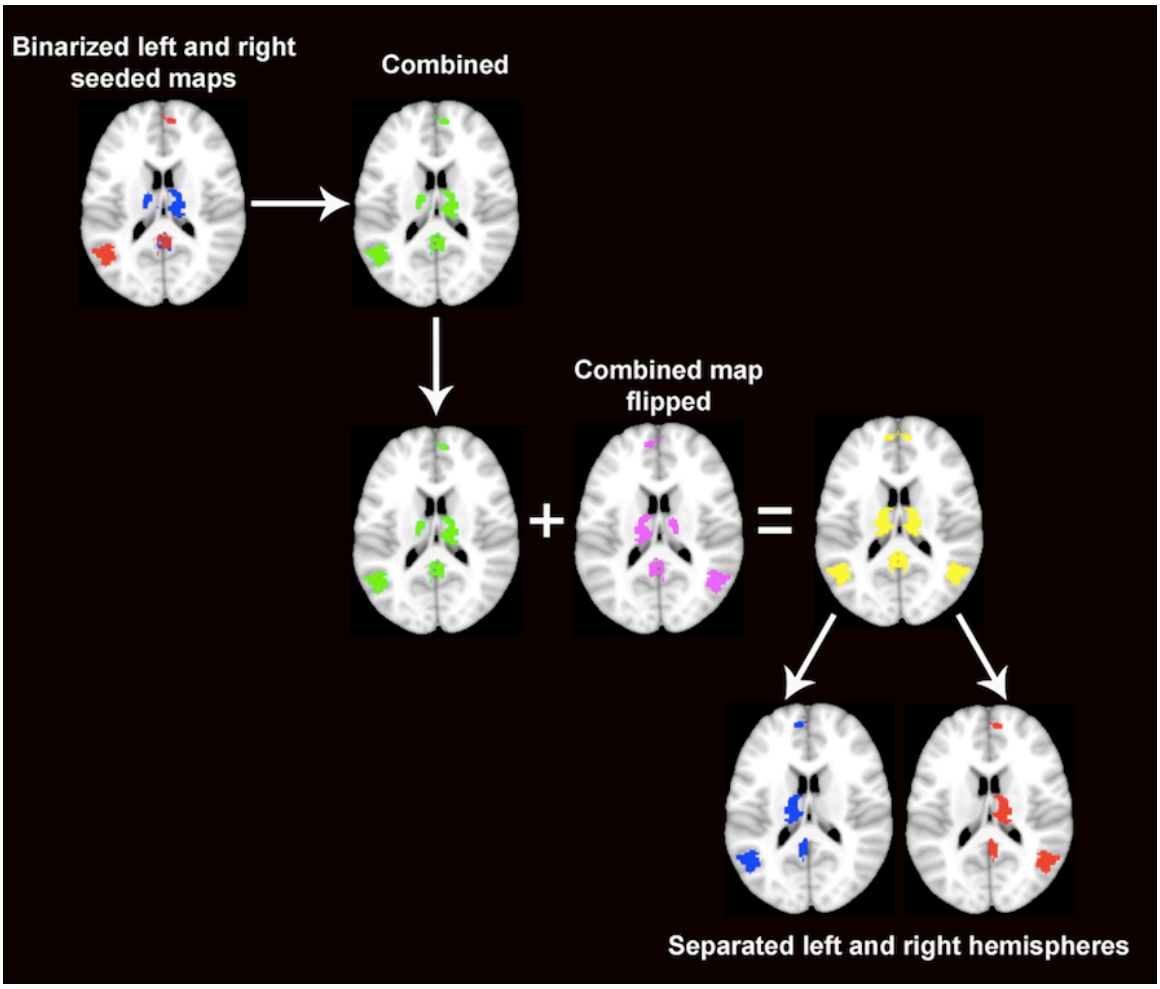

Fig. S3. ICN alterations with 10 preclinical *GRN* subjects with CDR total score of 0. Group difference maps show that widespread regions of increased intrinsic connectivity remain in 10 preclinical *GRN* compared with HC for all four networks studied. Left-seeded (yellow) and right-seeded (red) ICN increases generally overlapped (orange). Analyses were thresholded using joint probability distribution thresholding with a joint height and extent threshold of $p < 0.05$ corrected for multiple comparisons. Color bars represent t- scores, and statistical maps are on the Montreal Neurological Institute template brain. The left side of the axial and coronal images corresponds to the left side of the brain.

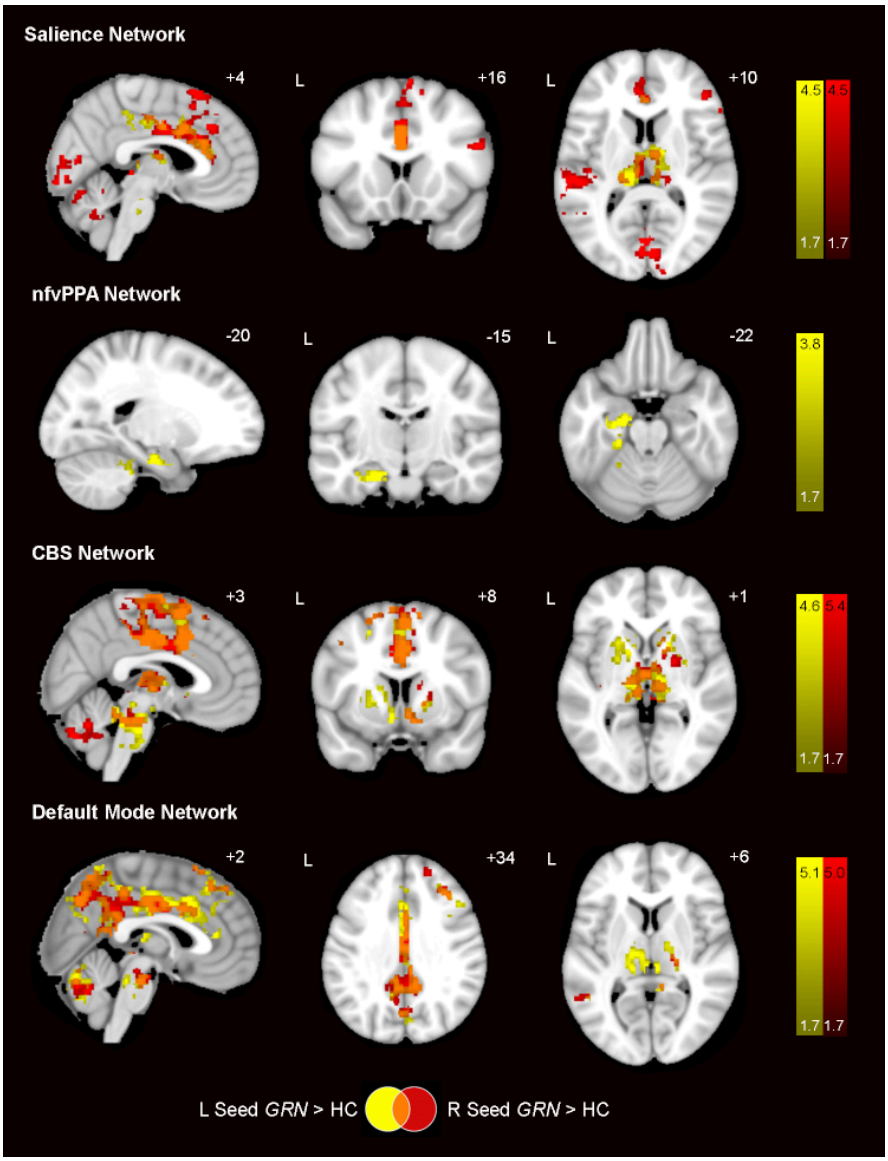

Fig. S4. ICN connectivity changes associated with increasing age for *GRN* carriers with CDR total score of 0. For the *GRN* carriers with CDR = 0, maps show regions of increasing connectivity with age compared to HC in left-seeded (yellow) and right-seeded (red) ICNs, especially within the thalamus. For the nfvPPA network, there were left-seeded (green) connectivity decreases with age. Analyses were thresholded using joint probability distribution thresholding with a joint height and extent threshold of $p < 0.05$ corrected for multiple comparisons. Color bars represent t- scores, and statistical maps are on the Montreal Neurological Institute template brain. The left side of the axial and coronal images corresponds to the left side of the brain.

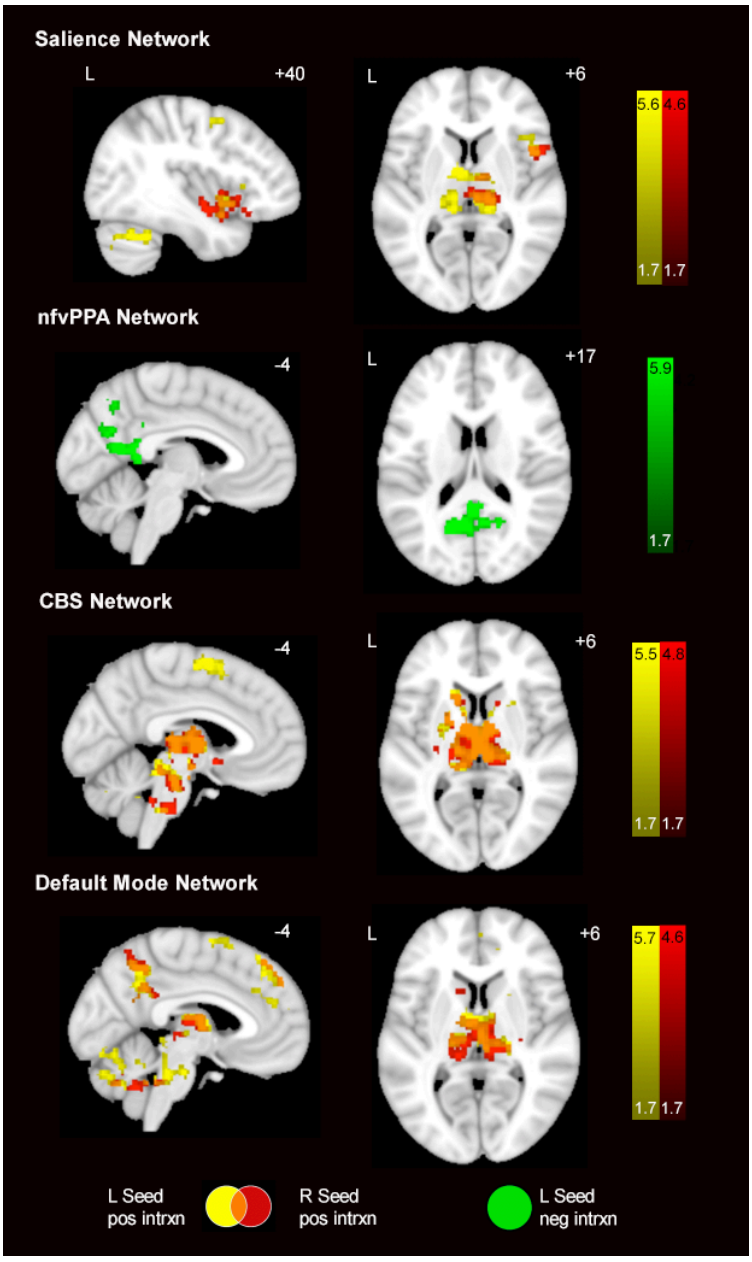

Fig. S5. Atrophy-adjusted comparisons of thalamic connectivity in presymptomatic and symptomatic *GRN* carriers. Mean WBD/gray matter w-scores extracted from the thalamic preclinical *GRN* > HC difference map in Fig. 4A, shows WBD hyperconnectivity in preclinical *GRN* with CDR = 0 and preclinical *GRN* with CDR = 0.5 and reduced connectivity in symptomatic *GRN* carriers. Error bars show 1 SEM.

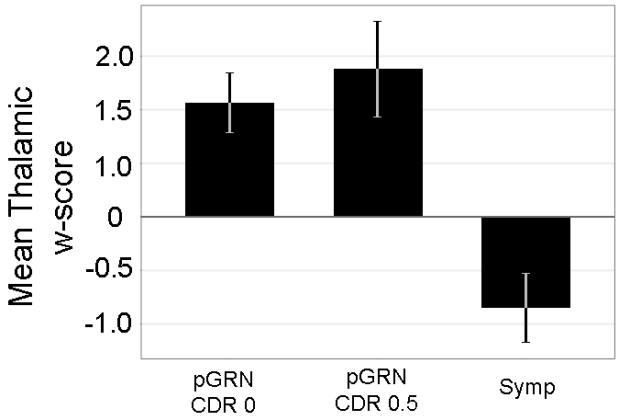

Fig. S6. Increased whole brain degree connectivity for *GRN* carriers with CDR total score of 0. Group difference map of *GRN* carriers with CDR 0 vs. HC demonstrates increases in WBD centrality. Analyses were thresholded using joint probability distribution thresholding with a joint height and extent threshold of $p < 0.05$ corrected for multiple comparisons. Color bars represent t- scores, and statistical maps are on the Montreal Neurological Institute template brain. The left side of the axial and coronal images corresponds to the left side of the brain.

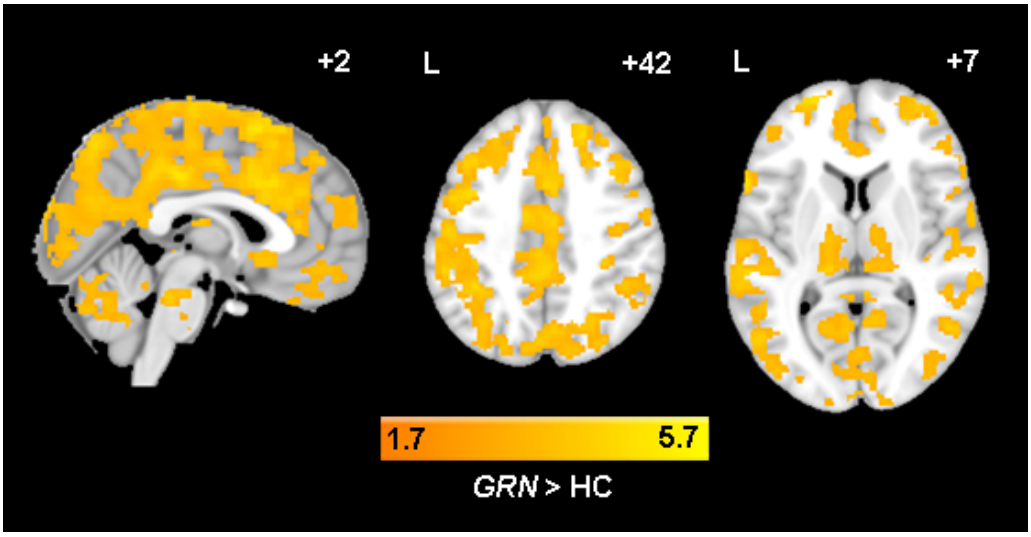

Fig. S7. Higher neuropsychiatric symptoms and depression scores correlate with lower salience network connectivity for *GRN* carriers with CDR total score of 0. (A) NPI and (B) GDS total scores correlated with reduced salience network connectivity in *GRN* carriers with CDR total score of 0. Weaker connectivity of the left (yellow) and the right (red) frontoinsula seeds to the voxels shown predicted greater (A) neuropsychiatric symptom severity and (B) depression severity. Results are displayed at a joint cluster and extent probability threshold of $p < 0.05$, corrected for multiple comparisons. Color bars represent t- scores, and statistical maps are on the Montreal Neurological Institute template brain. The left side of the axial and coronal images corresponds to the left side of the brain.

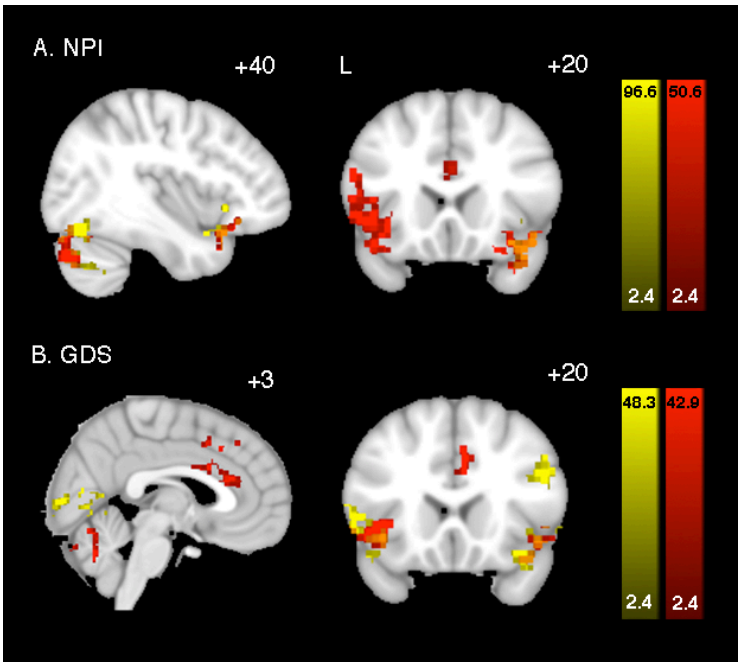

Fig. S8. Mean connectivity values with the thresholded preclinical *GRN* vs. HC maps. We extracted the mean connectivity beta value within the thresholded preclinical *GRN* vs. HC maps from Figure 2 and plotted each subject's connectivity vs. age. Age axis labels are omitted to prevent unwanted disclosure of genetic information to participants. Preclinical *GRN* with CDR = 0 are depicted as blue circles, preclinical *GRN* with CDR = 0.5 as blue dots, and HC as black circles. Fit lines are shown for visualization purposes only.

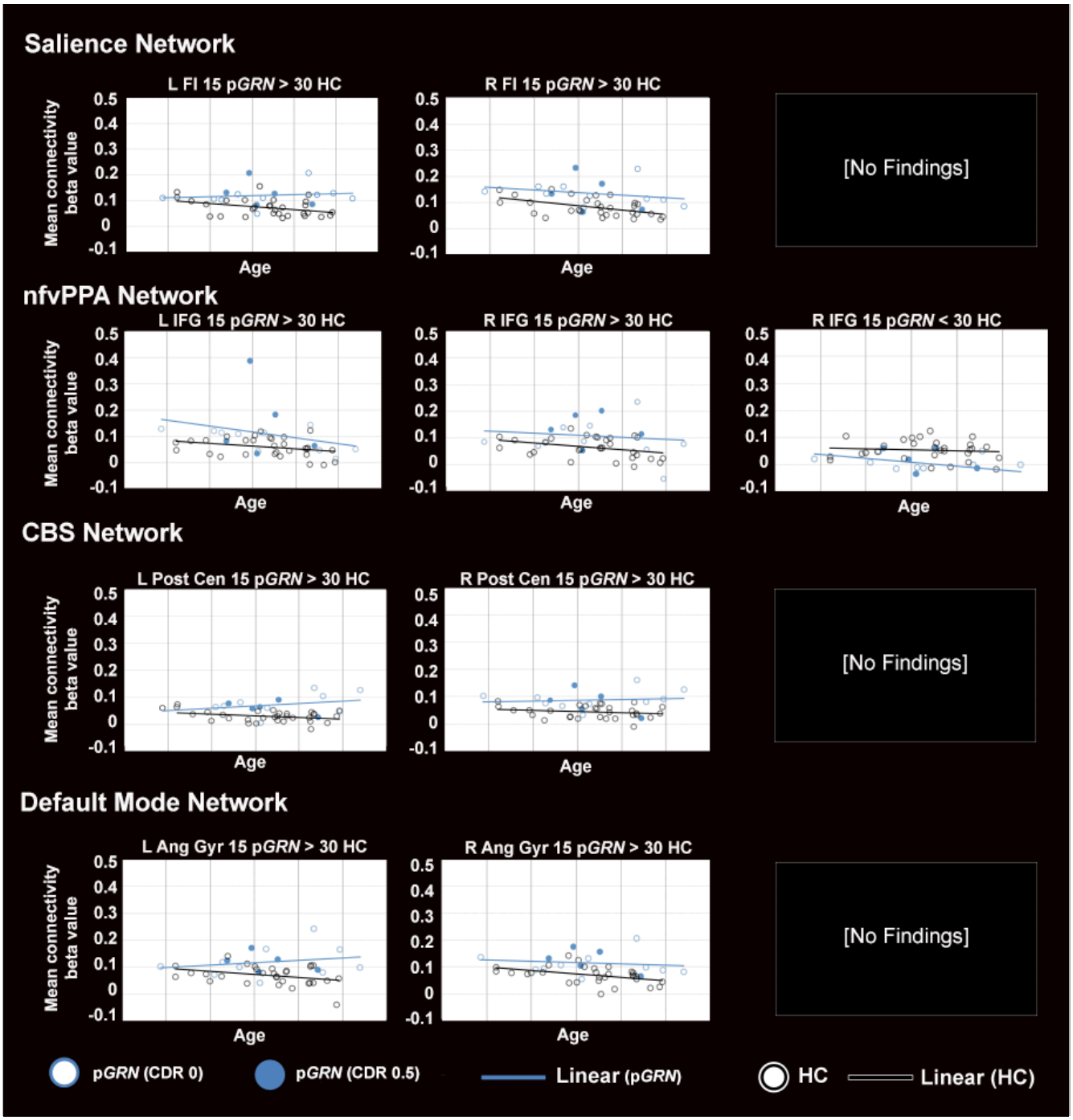

Table S1. Demographic comparison of *GRN* and HC for task-free fMRI analyses

	Healthy controls (n = 30)	***GRN* carriers (n = 15)**	**Test statistic, df**	**p**
M:F, *n*	14:16	6:9	$\chi^2 = 0.01, 1$	0.92
Handedness, L:R	6:24	3:12	$\chi^2 = 0.0, 1$	1.00
Age at MRI scan, years	53.3 (10.4)	53.3 (12.2)	t = -0.01, 24.5	0.99
Mean root-mean-square, translation (mm)	0.152 (0.088)	0.169 (0.127)	W = 229	0.93
Mean root-mean-square, rotation (degrees)	0.063 (0.031)	0.088 (0.067)	W = 255	0.48

Table S2. Clinical and demographic characteristics of symptomatic *GRN* carriers

	8 symptomatic *GRN* carriers
M:F, *n*	4:4
Handedness, L:R:A	0:8:0
Age at MRI scan, years	60.1 (6.2)
Education, years	16.5 (3.0)

Disease duration, years	2.0 (0.8)
MMSE	23.3 (5.9)
CDR total (median, range)	1 (0-2)
CDR, sum of boxes	5.3 (3.2)

Table S3. Demographic characteristics of gray matter w-score healthy controls

	HC2
M:F, *n*	116:172
Handedness, L:R:A	35:250:3
Age at MRI scan, years	66.3 (10.9)
Education, years	17.3 (2.2)

Table S4. Demographic characteristics of ICN w-score healthy controls

	HC3
M:F, *n*	64:101
Handedness, L:R:A	23:140:2
Age at MRI scan, years	66.8 (11.5)
Education, years	17.4 (2.2)

Mean root-mean-square, translation (mm)	0.23 (0.10)
Mean root-mean-square, rotation (degrees)	0.13 (0.06)

Table S5. Demographics and Neuropsychological Testing of *GRN* carriers with CDR total = 0

	Healthy controls (HC, n = 30)	**Preclinical *GRN* carriers (n = 11)**	**Test Statistic, df**	**p**
M:F, n	14:16	3:8	X = 1.2	0.26
Handedness, L:R:A	6:24:0	2:9:0	X = 0.02	0.90
Age at MRI scan, years	53.3 (10.4)	53.7 (13.6)	T = -0.08, 15	0.94
Education, years	16.0 (2.1)	16.7 (3.1)	T = -0.07, 14	0.51
CDR, sum of boxes	0 (0)	0.1 (0.2)	W = 120	**0.01**
Mini-Mental State Exam (max = 30)	29.2 (0.9)	28.3 (1.0)	W = 248	**0.01**
Stroop, color naming trial	96.1 (16.4)	83.3 (17.9)	T = 1.8, 10	0.10
NPI frequency x severity (max = 144)	4.1 (5.7)	6.0 (6.3)	W = 57.5	0.22
Geriatric Depression Scale (max = 30)	2.5 (2.4)	3.5 (2.7)	W = 97.5	0.20
Interpersonal Reactivity Index, fantasy	19.5 (6.7)	15.0 (4.9)	T = 1.9, 15	0.08

Interpersonal Reactivity Index, empathic concern	28.6 (3.5)	33.0 (2.4)	W = 16	**0.01**
Interpersonal Reactivity Index, perspective taking	24.2 (6.0)	30.5 (3.0)	T = -3.3, 18	**0.003**
Interpersonal Reactivity Index, personal distress	11.7 (3.9)	11.1 (3.1)	W = 72.5	0.75

Table S6. VBM of 17 preclinical *GRN* vs. 30 HC

Contrast	**Region containing peak voxel**	**BA**	**x,y,z**	**Peak T**	**Size**	**17 *GRN***	**11 *GRN* with CDR 0**
GRN < HC	L Cingulate Gyrus	23	-2,-4,33	5.62	479	X	
	R Superior Parietal Lobule	7	14,-70,57	5.23	94		X
	L Lingual Gyrus	18	-9,-57,-3	4.56	67		X
	R Supplementary Motor Area	6	9,0,66	4.50	31		X
	R Medial Superior Frontal Gyrus	9	9,48,45	4.39	63	X	
	L Middle Temporal Gyrus	37	-51,-57,12	4.26	58	X	
	R Insula	48	48,4,3	4.16	75	X	X
	R Middle Temporal Gyrus	21	68,-28,-8	4.12	94	X	
	L Supramarginal Gyrus	3	-57,-24,44	4.11	81	X	
	L Thalamus	NA	-3,-8,9	4.11	213	X	X
	L Supramarginal Gyrus	48	-63,-45,26	4.02	79	X	

	R Inferior Frontal Gyrus, Pars Opercularis	44	44,15,36	4.01	41	X	
	L Cuneus Cortex	18	-16,-69,26	3.99	99	X	
	L Superior Frontal Gyrus	10	-22,60,18	3.99	53	X	
	L Inferior Frontal Gyrus, Pars Triangularis	45	-54,22,3	3.96	108	X	
	R Superior Temporal Gyrus	22	64,-15,12	3.96	27		X
	L Gyrus Rectus	11	-6,62,-18	3.95	48	X	
	R Cuneus Cortex	7	9,-72,36	3.94	43	X	
	L Inferior Frontal Gyrus, Pars Triangularis	45	-44,46,10	3.93	53	X	
	R Superior Parietal Lobule	5	14,-57,68	3.92	39		X
	R Insula	48	34,9,4	3.86	43	X	X
	R Midcingulate Cortex	23	0,-4,32	3.86	37		X
	L Superior Frontal Gyrus, Pars Orbitalis	11	-24,56,-4	3.84	21	X	
	R Superior Frontal Gyrus, Pars Orbitalis	47	48,39,-14	3.81	27	X	
	L Precuneus	7	-14,-69,63	3.81	55	X	
	L Precentral Gyrus	44	-40,12,42	3.80	26	X	X

	L Insula	48	-46,14,-8	3.73	45	X	X
	L Middle Temporal Gyrus	39	-51,-69,22	3.69	23	X	
	L Middle Temporal Gyrus	21	-52,9,-24	3.68	42	X	
	L Fusiform Gyrus	37	-27,-51,-8	3.68	20		X
	L Middle Frontal Gyrus, Pars Orbitalis	46	-45,51,-9	3.63	40	X	
	R Inferior Frontal Gyrus, Pars Opercularis	48	52,14,9	3.61	33	X	
GRN > HC	R Pons	--	-9,-34,-38	4.55	59	X	X

Table S7. 15 preclinical *GRN* vs. 30 HC ICN comparisons with and without atrophy adjustment

Contrast	Region containing peak voxel	BA	x,y,z	Peak T	Size	Unadjusted	Atrophy Adjusted
Salience Network	L Mid Cingulate Cortex	24	0,14,38	4.90	3759		X
GRN > HC	L Heschl's Gyrus	48	-40,-24,8	4.74	203		X
	R Supplementary Motor Area	8	8,20,60	4.56	2104	X	
	L Superior Frontal Gyrus	8	-20,16,52	4.55	329		X
	L Mid Cingulate Cortex	23	-4,-28,34	4.47	2422	X	X
	L Medial Frontal Gyrus	32	-6,40,36	4.40	594	X	

	L Thalamus	--	-4,-16,16	4.33	865		X
	L Cerebellar Lobule VI	37	-32,-34,-32	4.29	303		X
	L Heschl's Gyrus	48	-40,-22,8	4.25	372		X
	R Inferior Frontal Gyrus, Pars Triangularis	45	50,30,4	4.13	966		X
	L Thalamus	--	-2,-14,14	3.87	878		X
	L Inferior Parietal Lobule	40	-42,-44,46	3.82	224		X
	R Parahippocampal Gyrus	20	28,-14,-24	3.79	213		X
	R Thalamus	--	10,-28,14	3.76	512	X	
	R Inferior Frontal Gyrus, Pars Triangularis	45	54,30,4	3.56	692	X	X
	R Cerebellar Lobule VI	37	26,-56,-18	3.52	501	X	X
	R Cerebellar Hemisphere Crus 1	--	38,-56,-36	3.32	920		X
	L Inferior Frontal Gyrus, Pars Orbitalis	47	-46,36,-6	3.23	415	X	X
	L Superior Temporal Gyrus	22	-60,-30,10	3.13	189		X
	R Putamen	11	22,20,-4	2.90	267		X
	L Cerebellar Hemisphere Crus 1	--	-14,-66,-28	2.78	180		X
nfvPPA network	L Medial Frontal Gyrus	32	-6,42,36	4.73	1170		X

GRN > HC	L Supplementary Motor Area	8	-6,24,62	3.91	703	X	
	R Middle Frontal Gyrus	9	40,12,44	3.79	195		X
	L Superior Frontal Gyrus	8	-20,10,58	3.69	672		X
	R Middle Frontal Gyrus	44	44,22,40	3.69	569		X
	R Thalamus	--	10,-28,14	3.52	565	X	X
	L Inferior Frontal Gyrus, Pars Triangularis	45	-48,34,22	3.31	480		X
	L Cerebellar Hemisphere Crus 2	--	-12,-74,-32	3.20	478		X
GRN < HC	R Cerebellar Lobule III	--	6,-42,-24	3.14	596	X	X
CBS network	L Caudate Nucleus	25	-6,12,-10	5.22	2588		X
GRN > HC	R Mid Cingulate Cortex	32	6,-20,42	5.13	3993	X	X
	L Heschl's Gyrus	48	-38,-26,10	4.92	455	X	X
	L Caudate Nucleus	25	-6,14,-10	4.63	3724	X	
	L Mid Cingulate Cortex	23	-8,-26,46	4.59	1975		X
	R Parahippocampal Gyrus	35	4,-22,-24	4.51	5368	X	X
	L Precentral Gyrus	6	-20,-12,62	4.20	1723	X	
	L Cerebellar Hemisphere Crus 1	--	-38,-68,-28	4.11	248		X
	L Mid Cingulate Cortex	24	0,14,38	4.11	170		X
	L Postcentral Gyrus	4	-18,-30,64	4.07	226		X

	L Superior Temporal Gyrus	42	-58,-40,14	4.04	367	X	X
	L Parahippocampal Gyrus	20	-32,-22,-24	4.04	1080		X
	R Parahippocampal Gyrus	20	32,-12,-26	3.96	326		X
	R Middle Temporal Gyrus	21	66,-32,-4	3.78	210		X
	L Gyrus Rectus	11	0,42,-22	3.68	176		X
	R Mid Cingulate Cortex	23	4,-40,34	3.66	375		X
	L Cerebellar Hemisphere Crus 1	--	-16,-84,-20	3.65	1242	X	X
	R Parahippocampal Gyrus	37	26,-36,-6	3.64	356		X
	R Vermis Lobule IX	--	0,-52,-38	3.37	402		X
	R Cerebellar Hemisphere Crus 2	--	42,-44,-42	3.26	236		X
	L Cerebellar Lobule IX	--	-4,-54,-36	3.24	369	X	
	R Postcentral Gyrus	3	42,-16,40	3.14	171		X
	R Middle Temporal Gyrus	21	64,-30,-6	3.03	221		X
	R Precentral Gyrus	6	18,-20,72	2.99	212		X
DMN	L Mid Cingulate Cortex	23	-4,-34,40	6.16	6300		X
GRN > HC	L Precuneus	7	0,-68,40	4.71	4768	X	
	R Medial Frontal Gyrus	8	4,30,52	4.70	4193	X	
	R Superior Frontal Gyrus	6	16,6,66	4.65	5355		X
	L Middle Temporal Gyrus	39	-46,-68,22	4.60	857		X

	R Inferior Temporal Gyrus	20	60,-26,-26	4.45	353		X
	L Middle Frontal Gyrus	44	-38,26,36	4.30	356		X
	L Middle Temporal Gyrus	21	-46,-56,14	4.27	326		X
	R Cerebellar Hemisphere Crus 1	--	32,-58,-36	4.14	1944	X	X
	L Cerebellar Lobule VI	--	-40,-56,-26	4.05	1857	X	X
	R Putamen	--	22,0,10	3.81	220		X
	L Putamen	48	-22,12,6	3.63	214		X
	L Inferior Frontal Gyrus, Pars Orbitalis	47	-48,30,-6	3.57	197		X
	L Inferior Parietal Lobule	40	-38,-54,48	3.44	249		X
	L Middle Temporal Gyrus	39	-46,-68,20	3.39	495	X	
	L Cerebellar Hemisphere Crus 1	--	-34,-54,-38	3.38	341		X
	R Parahippocampal Gyrus	20	34,-24,-18	2.80	180		X
	R Parahippocampal Gyrus	20	34,-18,-18	2.75	240		X

Table S8. ICN alterations with 10 preclinical *GRN* subjects (CDR total = 0) vs. 30 HC

Contrast	**Region containing peak voxel**	**BA**	**x,y,z**	**Peak T**	**Size**
Salience Network	L Mid Cingulate Cortex	24	0,12,34	4.54	1144
GRN > HC	L Anterior Cingulate Cortex	24	-4,26,28	4.53	1607

	Pons	--	14,-28,-30	4.25	721
	R Inferior Temporal Gyrus	37	50,-62,-14	3.95	3296
	R Inferior Frontal Gyrus, Pars Orbitalis	47	54,34,-8	3.62	623
	L Thalamus	--	-14,-32,8	3.40	937
	R Lingual Gyrus	27	10,-36,2	3.29	898
	L Superior Temporal Gyrus	41	-48,-30,12	3.19	328
	R Lingual Gyrus	37	30,-46,-6	3.16	385
nfvPPA network *GRN* > HC	L Parahippocampal Gyrus	35	-20,-16,-22	3.78	359
CBS network	R Mid Cingulate Cortex	24	0,14,32	5.41	4957
GRN > HC	L Mid Cingulate Cortex	24	0,14,36	4.62	3265
	R Cerebellar Lobule XIII	--	32,-42,-40	4.47	594
	L Thalamus	--	-14,-22,10	4.11	2196
	L Superior Temporal Gyrus	41	-48,-30,10	4.06	359
	Pons	--	2,-24,-24	4.00	4180
	Pons	--	14,-28,-28	4.00	2104
	R Putamen	--	32,-2,-4	3.65	331
DMN	R Superior Frontal Gyrus	8	20,24,58	5.10	5628

GRN > HC	R Mid Cingulate Cortex	23	14,-48,34	5.03	2983
	R Cerebellar Hemisphere Crus 1	37	44,-48,-26	4.49	2471
	L Middle Temporal Gyrus	21	-46,-56,16	4.38	449
	R Medial Frontal Gyrus	9	8,48,46	4.20	852
	R Cerebellar Hemisphere Crus 1	37	46,-50,-26	4.03	1346
	L Middle Temporal Gyrus	39	-44,-68,20	3.96	407
	R Parahippocampal Gyrus	20	32,-26,-18	3.86	473

Table S9. Interaction of group and age on ICN connectivity for 15 preclinical *GRN* vs. 30 HC

Contrast	**Region containing peak voxel**	**BA**	**x,y,z**	**Peak T**	**Size**
Regions where preclinical *GRN* show SN increases with age	R Inferior Frontal Gyrus, Pars Opercularis	48	48,10,8	4.74	856
	R Cerebellar Lobules IV, V	37	20,-42,-22	4.21	3076
	R Thalamus	--	8,-8,10	4.04	1248
	R Middle Frontal Gyrus	46	38,36,36	3.90	384
	R Cerebellar Lobule VI	18	16,-68,-18	3.83	1436
	R Inferior Frontal Gyrus, Pars Opercularis	44	54,14,22	3.64	648
	R Thalamus	--	16,-6,12	3.61	370

nfvPPA network decreases with age	R Lingual Gyrus	27	8,-44,4	5.05	1264
CBS network increases with age	L Cerebellar Lobules IV, V	27	-8,-34,-10	4.93	2884
	Thalamus	--	0,-10,-2	4.33	2260
	L Supplementary Motor Area	6	-6,-4,64	3.95	465
	R Cerebellar Hemisphere Crus 1	--	42,-62,-32	3.68	384
CBS network decreases with age	R Cerebellar Hemisphere Crus 1	--	36,-78,-22	4.21	348
	R Precuneus	30	2,-50,18	3.52	347
DMN increases with age	R Medial Frontal Gyrus	10	6,60,28	4.28	429
	R Thalamus	--	8,-6,10	4.20	1312
	R Cerebellar Lobule VI	18	16,-68,-18	3.93	3339
	R Thalamus	--	6,-6,12	3.65	1274
	L Cerebellar Lobule VIIB	--	-8,-72,-38	3.41	407
	R Cerebellar Lobule IX	--	4,-56,-40	3.02	453

Table S10. Whole brain degree connectivity in preclinical *GRN* vs. 30 HC

Contrast	Region containing peak voxel	BA	x,y,z	Peak T	Size	With CDR 0.5	Without CDR 0.5
GRN > HC	L Middle Frontal Gyrus	9	-34,16,52	5.6	26460	X	X
	R Middle Temporal Gyrus	20	60,-38,-10	4.23	750	X	
	R Thalamus	--	10,-24,16	3.76	1102	X	