Structural Neuroimaging of Anorexia Nervosa: Future Directions in the Quest for Mechanisms Underlying Dynamic Alterations

Supplemental Information

Supplemental References

Structural MRI studies counted in Figure 2

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Table S1: Summary of published DTI studies in AN (until 7/2017). Complete references are provided above.* denotes studies that included analyses of WM connectivity. Summaries of main findings are limited to primary analyses of anisotropy/diffusivity and WM connectivity and do not include supplementary analyses of relationships with clinical variables. Data on psychotropic medication and psychiatric comorbidities are given in numbers of AN patients.

author	sample size	AN subtype	age (years) +/-SD (AN/HC)	DOI ±SD (years)	medication	psychiatric comorbidities	time start of realimentation - scanning	image acquisition (tesla/ b/ gradient directions/ resolution)	white matter volume	DTI software	parameters
Kazlouski et al., 2011	16 acAN, 17 HC	mixed	acAN 23.9 ±7, HC 25.1±4	7.5±8	8 of 16	8 of 16 (DD)	1-2 weeks	3T, b n/a, 25 directions, 3.5mm with 0.5 mm gap	no group difference	SPM, DTIStudio	FA, ADC
FA: AN < HC in bilateral fimbria-fornix, fronto-occipital and posterior cingulum.											
Frieling et al., 2012	12 acAN, 9 recAN, 20 HC	only restrictive	acAN 26.8±6.9, recAN 27.4±5.3, HC 24.8±2.6	n/a	n/a	n/a	n/a	3T, b=1000 s/mm², 15 directions, 4mm thickness no gap	n/a	SPM	FA, ADC
FA: AN < HC in bilateral posterior thalamic radiation, left mediodorsal thalamus, bilateral posterior coronal radiata, left middle cerebellar peduncle, left superior longitudinal fasciculus.											
Frank et al., 2013	19 acAN, 22 HC	mixed	acAN 15.4±1.4, HC 14.8±1.8	n/a	11 of 19	5 of 19	min 1 week	3T, b n/a, 25 directions, 3.5mm thickness with 0.5 mm gap	WM volume greater in AN than HC in several brain regions	SPM, NordicICE	FA, ADC
FA: AN < HC in left fornix, bilateral cingulum, right forcepts major, right superior and left posterior corona radiata. AN > HC in left superior longitudinal fasciculus, bilateral anterior corona radiata and bilateral inferior fronto-occipital fasciculus. ADC: AN >HC in left fornix, right corpus callosum, right corticospinal tract, right posterior corona radiata, bilateral corticopontine tract, bilateral superior longitudinal fasciculus.											
Yau et al., 2013	12 recAN, 10 HC	only restrictive	recAN 28.7±7.9, HC 26.7±5.4	6±5	none	none	weight restored	3T, b=1000 s/mm², 55 directions, 2.5mm isotropic, n/a	n/a	FSL	FA, MD, RD, AD
FA: no group differences. MD: AN < HC in left superior frontal WM including corona radiata (superior and posterior), corpus callosum (body and bilateral splenium), posterior limb of capsula interna, left superior longitudinal fasciculus, left posterior cingulum, precuneus and superior parietal WM, left dorsal cingulum, right precuneus and posterior corona radiata, right posterior cingulum and posterior corona radiata. In all of these regions, AD and/or RD was reduced in AN relative to HC.											
Via et al., 2014	19 acAN, 19 HC	only restrictive	acAN 28.4±9.6, HC 28.6±8.6	3+/-3	5 of 19	n/a	min 1 week	1.5T, b=1000 s/mm², 25 directions, 5mm thickness no gap	no group difference	FSL, TBSS	FA, MD
FA: AN < HC in the parietal portion of the superior longitudinal fasciculus and fornix. MD: AN > HC in the superior longitudinal fasciculus and fornix. Decreased FA in the superior longitudinal fasciculus was driven largely by increased RD, while increased MD in the fornix was driven by both increased AD and RD.											
Nagahara et al., 2014	17 acAN, 18 HC	n/a	acAN 23.8±6.7, HC 26.2±5.6	5±5	6 of 17	4 of 17 (DD)	n/a	3T, b=1000 s/mm², 32 directions, 2mm thickness no gap	n/a	FSL, TBSS	FA, MD
FA: AN < HC in left cerebellum. MD: AN > HC in the anterior body of the fornix. AN < HC in the right corpus callosum and right superior longitudinal fasciculus. Group differences did not remain significant after controlling for medication.											
Shott et al., 2015*	24 recAN, 24 HC	only restrictive	recAN 30.3±8.1 , HC 27.4 ± 6.3	6±5	6 of 24	9 of 24 (3 DD, 4 AnxD, 2 DD/AD)	weight restored	n/a, b=1000 s/mm², 25 directions, 2.6mm thickness no gap	no group difference	FSL, Probtrackx2	FA, MD, RD, AD
FA: AN < HC in anterior coronata radiata, capsula interna, cerebellum (corticopontine tract, inferior and middle peduncle), corpus callosum, anterior thalamic radiation, inferior fronto-occipital, unicate fasciculus. Probabilistic tractography suggested increased WM connectivity between bilateral insula and ventral striatum, left insula and middle orbitofrontal cortex and right insula to gyrus rectus and medial orbitofrontal cortex.											
Hayes et al., 2015*	8 acAN, 8 HC	mixed	acAN 35±11, HC 36±9	16±6	8 of 8	7 of 8	n/a	3T, b=1000s/mm², 60 directions, 0.94*0.94*3.0 mm³, n/a	n/a	FSL, 3D Slicer	FA, RD, AD
FA: AN < HC in bilateral anterior limb of capsula interna, left inferior fronto-occipital fasciculus, right anterior cingulum (with corresponding decreases in AD and increases in RD). AN > HC in the left fornix crus. Deterministic multitensor tractography suggested WM connectivity to be increased in prefrontal and left occipitoparietal corticies and decreased in thalamus in AN relative to HC.											
Travis et al., 2015	15 acAN, 15 HC	only restrictive	acAN 16.6±1.4, HC 17.1±1.3	1±1	2 of 15	n/a	n/a (outpatients)	3T, b=2500 s/mm², 96 directions, 2mm³ isotropic, n/a	n/a	MrDiffusion	FA
FA: AN < HC in 4 tracts (right anterior superior longitudinal fasciculus, bilateral fibra-fornix, motor subdivision of corpus callosum). AN > HC in 2 tracts (right anterior thalamic radiation, left anterior superior longitudinal fasciculus). T1 relaxometry also revealed evidence suggestive of reduced myelin content in AN in 11 out of the 26 investigated WM tracts and subdivisions of the corpus callosum.											
Pfuhl, King et al., 2016	35 acAN, 32 recAN, 62 HC	mixed	acAN 16.1±2.8 , recAN 22.5±3, HC 16.4±2.6	n/a	none	2 of 35 (acAN), 7 of 32 (recAN)	within 96h	3T, b=1300 s/mm², 30 directions, 2.4 mm isotropic no gap	no group difference	FSL, TRACULA	FA, MD, RD, AD
No group differences in FA, MD, RD, AD after correction for multiple comparisons.											

author	sample size	AN subtype	age (years) +/-SD (AN/HC)	DOI ±SD (years)	medication	psychiatric comorbidities	time start of realimentation - scanning	image acquisition (tesla/ b/ gradient directions/ resolution)	white matter volume	DTI software	parameters
Cha et al., 2016*	22 acAN, 18 HC	mixed	acAN 19.5±2.42, HC 20.5±2.95	n/a	none	6 of 22 (3 DD, 3 SP)	min 1 week	1.5T, b=800 s/mm², 16 directions, 2mm isotropic no gap	n/a	FSL, TBSS	FA
FA: AN > HC in the fronto-accumbal WM region of interest near the lateral orbitofrontal cortex and nucleus accumbens both before and after weight restoration. Probabilistic tractography suggested increased WM connectivity between nucleus accumbens and lateral orbitofrontal cortex in both hemispheres both before and after weight restoration.											
Vogel et al., 2016	22 acAN , 21 HC	mixed	acAN 15+-1.6, HC 15+-1.0	1+-1	2 of 20	4 of 22 (1 DD, 2 AnxD, 1 DD/AD)	longitudinal observation at admission and discharge	3T, b=1000 s/mm², 30 directions, Protocol 1: 2mm³ isotropic, Protocol 2: 2x2mm² /3.5 mm thickness and 10% gap	n/a	FSL, TBSS	FA, MD, RD, AD
FA: AN > HC in the bilateral superior corona radiata, anterior corpus callosum, anterior and posterior thalamic radiation, anterior and posterior internal capsule, and the left inferior longitudinal fasciculus at admission using voxelwise TBSS. Elevated FA at admission was associated with reduced MD and RD, but not AD. No group differences were present at discharge using voxelwise TBSS analysis, but FA remained elevated in ROI analysis.											
Zhang et al., 2016*	24 recAN, 29 BDD, 31 HC	n/a	recAN 21.3±4.5 , BDD 23.2±5, HC 20.9±3.91	6±5 / 10±6	none	n/a	weight restored	3T, b=1000 s/mm², 64 directions, n/a	n/a	DTIStudio	n/a
No group differences in total fiber count. Analysis of WM connectivity revealed no group differences in network modularity using a standard metric (Q). Using a custom technique (Path Length Associated Community Estimation), abnormal modularity involving frontal, basal ganglia, and posterior cingulate nodes was observed in weight-restored AN patients. No standard analyses of anisotropy or diffusivity.											
Canna et al., 2016	15 acAN, 13 BN, 16 HC	n/a	acAN 25.3±1.6, BN 27.2±2, HC: 26:1±3.5	n/a	none	none	n/a	3T, b=1000 s/mm², 16 directions, 2mm³ isotropic with 0.4 mm gap	n/a	DTIStudio	FA
FA: Analyses focused only on corpus callosum. No group differences were significant.											
Frank et al., 2016*	26 acAN, 25 BN, 26 HC	only restrictive	acAN= 23.2±5.3, BN= 24.6±4.2, HC 24.4±3.5	7±6 / 7±5	16 of 26	19 of 26 (4 DD, 5 AnxD, 10 DD/AD)	1-2 weeks	3T, b=1000 s/mm², 25 directions, 2.6mm thickness no gap	n/a	DTIStudio	FA
FA: Analyses focused on fiber paths belonging to a priori-defined brain taste-reward network. FA was reduced in AN relative to HC (AN < HC) from the left ventral anterior insula/gyrus rectus to ventral striatum, the left posterior insula to middle OFC, the right middle OFC to hypothalamus, the right central nucleus of amygdala to hypothalamus, the left dorsal anterior insula to ventral striatum, the right dorsal anterior insula to gyrus rectus, the bilateral posterior insula to ventral striatum, the left medial OFC to hypothalamus, the right medial OFC to ventral striatum and the left gyrus rectus to PFC. WM connection strength was increased (AN > HC) in pathways between insula, orbitofrontal cortex and ventral striatum, but decreased (AN < HC) from orbitofrontal cortex and amygdala to hypothalamus.											
Olivo et al., 2017	1 acAN, 11 EDNOS, 24 HC	only restrictive	acAN= 16, EDNOS= 14.9±1.6, HC 14.1	n/a	none	6 of 12 (6 DD, 1 AnxD, 2 PTSD, 1 OCD)	longitudinal study: baseline upon diagnosis and follow-up one year later	3T, b n/a, 48 directions, 1.75 mm³ isotropic, n/a	n/a	FSL, TBSS	FA, MD, RD, AD
FA: AN/EDNOS < HC at baseline in corpus callosum, corona radiata and posterior thalamic radiation, but no group differences at follow-up. RD: AN/EDNOS < HC at baseline in the same regions, but no group differences at follow-up.											
Kaufmann et al., 2017	Pre-Study: 32 HC Main Study: 25 acAN, 25 HC	n/a	acAN= 22.8±4.8, HC=23.36±3.4	6.8±4.9	11 of 25	n/a	min 2 weeks	3T, b=1000,64 directions, 2 mm³ isotropic, n/a	no group difference	FSL, TBSS, TRACULA	FA, RD, AD
In a pre-study, the authors first demonstrated an inverse relationship between FA in the fornix and volumes of the surrounding third and lateral ventricles. In the main study, FA was reduced in the fornix in AN (AN < HC), but this group difference was significantly smaller after controlling for ventricular volumes and disappeared completely after correcting for free-water.											
Gaudio et al., 2017	14 acAN, 15 HC	only restrictive	acAN=15.7±1.6, HC 16.3±1.5	.4±.2	none	none	min 1 week	1.5 T, b=1000, 48directions, 2.5 mm thickness no gap	no group difference	FSL, TBSS	FA, MD, RD, AD
FA: AN < HC in the left anterior and superior corona radiata and left superior longitudinal fasciculus. AD: AN < HC in the superior longitudinal fasciculus bilaterally and the left superior and anterior corona radiata. No group differences in RD or MD.											

Abbreviations: acAN, acute, underweight phase AN; EDNOS, eating disorder not otherwise specified; recAN, weight recovered AN; HC, healthy control; DOI, duration of illness; FA, fractional anisotropy; ADC, apparent diffusion coefficient; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity ADHD, attention-deficit/hyperactivity disorder; BDD, body dysmorphic disorder; BN, bulimia nervosa; DOI, duration of illness; DD, depressive disorder; AnxD, anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; SP, specific phobia.