Tables

Progression of neuroanatomical abnormalities after first-episode of psychosis: A 3-year longitudinal sMRI study

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Table 1: Longitudinal neuroimaging studies that examined volumetric progression of ventricles, subcortical structures, total grey and white matter after first-episode psychosis or schizophrenia

Reference	Diagnosis, n, Age (SD) in years		DOI, DUP	Medications/Duration of Treatment		Approx. Average Follow-up period	Study Re-recruitment Rate (%)	MRI/Processing Method	Brain Regions Examined	Findings in relation to ventricles, subcortical structures, total grey/white matter and cortical thickness change in patients
	Patients	Controls		Duration of Treatment prior to baseline Scan	Treatment during follow-up					
DeLisi *et al.* 1997†	SCZ; n=50/ (27.4±7.0)	n=20/ (26.5±5.0)	DUP: 48.8 weeks	unclear	FGA, SGA, OM	4 years	50.4	1.5 T/ ANALYZE	Whole hemisphere, temporal lobes, superior temporal gyrus, hippocampus, amygdala, caudate, corpus callosum, cerebellum and lateral ventricles	1. Left ventricular enlargement in patients 2. Greater bilateral caudate reduction in controls † 3. No significant hippocampal, amygdala and caudate volume change in patients
Wood *et al.* 2001	het; n=30/ (21.8 ± 3.6)	n=26/ (23.8±7.9)	Median DUP: 4.2weeks	up to the day of scan	FGA, SGA	2 years	100.0	1.5 T/ ANALYZE	Hippocampus, temporal lobe, whole brain	No significant hippocampal volume changes were found in patients
Lieberman *et al.* 2001	SCZ; n=107/ (31.17±6.70)	n=20/ (26.00±6.78)	DUP: 68.5 weeks	Naïve	FGA, SGA, OM	18 months	50.4	1.0 T/semi-automated computer mensuration system	Cortex, ventricles, Caudate, Hippocampus	1. Ventricular enlargement in patients 2. No hippocampal volume change in patients 3. Significant caudate volume increase in patients
Puri *et al.* 2001	SCZ; n=24/ (28.47±8.45)	n=12/ (27.92±6.14)	DUP: 59.7 weeks	<12 weeks	FGA, SGA	8 months	100.0	1.0 T/semi-automated computerised technique using image registration and subtraction approaches	Lateral ventricles	1. No significant mean changes in ventricular volume in patients overtime 2. Highly variable ventricular volumes
Lang *et al.* 2001	SCZ; n=24/ (22.90±8.45) SCZ; chronic; n=24/ (38.40±11.60)	n=12/ (27.70±7.20)	unclear	<12 weeks 307.1 weeks	SGA	1 year	83.6	1.5 T/ manually segmentation with the interactive Shareware (NIH Image, v.1.61 ppc)	Basal Ganglia	No significant longitudinal basal ganglia volume changes found in the FEP patients
Cahn *et al.* 2002	SCZ; n=34/ (26.20±5.31)	n=36/ (24.5±5.80)	DOI: 72.8 weeks	<16 weeks	FGA, SGA	1 year	92.9	1.5 T/ in-house semi-automated software using intensity histogram analysis algorithms	Total brain, ventricles, cerebellum, cerebral grey and white matter	1. Grey matter volume reduction in patients 2. Lateral ventricular enlargement in patients
Massana *et al.* 2005	SCZ; n=11/ (23.0±4.0)	-	unclear	Naïve	SGA	3 months	100.0	1.5 T /optimised voxel-based morphometry	Basal ganglia, ventricles, cerebellum, cerebral grey and white matter	1. Significant grey matter increase in the left accumbens and the left caudate nuclei 2. No significant ventricular, total cerebral grey and white matter volume changes were demonstrated
Theberge *et al.* 2007*	SCZ; n=16/ (25.0±8.0)	n=16/ (29.0 ±12.0)	DOI: 96.2 weeks DUP: 96.2 weeks	Naïve	FGA, SGA, OM	10 months 30 months	100.0	4T/ Voxel-based morphometry	Whole brain	Greater reductions in total grey mater, right caudate and right thalamus were found in patients
Nakamura *et al.* 2007	FESCZ; n=17/ (26.0±6.80)	n=26/ (25.1 ±4.0)	unclear	3 weeks	FGA, SGA, OM	1.5 years	64.6	1.5 T/ Expectation Maximisation Segmentation	Neocortical Grey Matter, ventricles	1.Significant longitudinal increase of neocortical grey matter volume was observed in the FEAFF group relative to controls

	FEAFF n=21/ (23.70±3.20)			1 week				(EMS) toolbox		2. In the FESCZ group, neocortical grey matter volume reductions were observed in the frontal and temporal regions with enlargement of lateral ventricles which did not reach statistical significance
Glenthoj *et al.* 2007	SCZ;Risperidone; n=11/ (25.7±5.2) SCZ; Zuclopenthixol; n=8/ (26.1±5.3)	n=16/ (29.0 ±12.0)	DUP: 74.8 weeks DUP: 56.4 weeks	Naïve	FGA, SGA	12 weeks	100.0	1.5 T/Manual and semi-automated approaches were used (DISPLAY software)	Basal Ganglia	1. Significant volume increase in the putamen was demonstrated in patients treated with risperidone 2. Altered asymmetry in caudate volume of patients was observed, with the left caudate being marginally smaller in volume than the right
Deng *et al.* 2009	SCZ; n=20/ (29.9±13.5)	n=11/ (28.0±11.7)	Median DUP: 17.1 weeks	Naïve	FGA, SGA	3 weeks	100.0	1.5 T/ Expectation Maximisation Segmentation (EMS) toolbox	multiple brain regions	Grey matter volume increase in the right caudate and thalamus in patients
Rais *et al.* 2010	SCZ; Cannabis+n=19/ (29.44±8.21) SCZ; Cannabis- n=32/ (23.28±5.10)	n=31/ (24.72±6.66)	DOI: 61.3 weeks DOI: 50.1 weeks	17 weeks 11 weeks	FGA, SGA	5 years	92.9	1.5T /The CLASP algorithm was used to estimate change in cortical thickness for every vertex in individual space, then transformed to the ICBM template for visualisation.	multiple brain regions	Progressive cortical thinning of the right supplementary motor cortex, inferior frontal cortex, superior temporal gyrus, angular gyrus, occipital and parietal lobe was found in patients compared to controls after controlling for cannabis use.
de Castro-Manglano *et al.* 2011	het; n=22/ (18.50± 4.00)	n=17/ (18.30 ±5.80)	DUP: 10 weeks	28.5 weeks	FGA, SGA, OM	3 years	90.7	1.5T/ Voxel-based morphometry	Whole brain	No significant longitudinal thalamic volume changes observed
Boonstra *et al.* 2011	SCZ; continued Treatment; n=8/ (29.56±5.72) SCZ; discontinued Treatment; n=8/ (26.20±5.70)	n=20/ (27.97±5.63)	DUP: 73.8 weeks DUP: 49.9 weeks	unclear	SGA	1 year	100.0	1.5 T/ in-house semi-automated software using intensity histogram analysis algorithms and manual tracing for the basal ganglia	Cerebral grey and white matter, ventricles, cerebellum, basal ganglia	1. Significant reduction in volume of cerebral grey matter and caudate was observed overtime in patients relative to controls 2. Significant volume reductions in the nucleus accumbens and putamen in patients who discontinued antipsychotic medication, whereas increases were found in patients who continued antipsychotic medication 3. No significant progressive ventricular changes were found
Ebdrup *et al.* 2011	SCZ; Low dose Treatment; n=13/ (26.20±5.70) SCZ; High dose Treatment; n=9/ (27.80±5.10)	n=28/ (28.40±6.00)	DUI: 266.8 weeks DUI: 133.6 weeks	Naïve	SGA	6 months	61.7	3 T/ DARTEL (diffeomorphic anatomical registration through exponentiated lie Algebra) with VBM5 toolbox	Striatum, hippocampus and ventricles	1. Significant progressive bilateral striatal and hippocampal volume reductions were observed in patients relative to controls. 2. The striatal volume loss was most pronounced in the low dose treatment group. 3. Hippocampal volume reductions were more pronounced in the high dose treatment group relative to controls. 4. No significant changes in ventricular, total cerebral grey and white matter were observed in patients.
Schaufelberger *et al.* 2011	SCZ; n=39/ (29.50±9.00)	n=52/ (31.80 ±8.80)	unclear	unclear	FGA,SGA	18 months	61.1	1.5T/ Voxel-based morphometry and manual ventricular tracing with MRICRO v.1.40 software	Whole brain	1. Significant volume increase in right hippocampal volume 2. No significant longitudinal ventricular changes observed 3. No significant change in global brain tissues
Andreasen *et al.*	SCZ; n=202/	n=125/	unclear	Naïve	FGA, SGA, OM	7years	65.5	1.5 T♦/BRAINS2 AutoWorkup	Global and lobular grey and white,	1. Increase in lateral ventricular volume overtime in patients

2011	(24.56±7.14)	(29.69±8.37)		(50% of sample)				software	ventricles, thalamus, putamen, caudate	2. Decrease in thalamic volume overtime in patients 3. No significant volume changes observed in the caudate and putamen.
Asami *et al*. 2012	SCZ; n=33/ (22.50±6.70)	n=36/ (22.90 ±3.80)	DOI: 19.5 weeks	<20 weeks	FGA, SGA, OM	1.5 years	63.8	1.5T/ Voxel-based morphometry	Superior temporal gyrus, amygdala, hippocampus, bilateral Heschl's gyrus, anterior and posterior cingulate gyrus	No significant longitudinal changes in amygdala and hippocampus found
Roiz-Santiánez *et al.* 2014	SCZ; n=109/ (29.44±8.21)	n=76/ (27.80±7.73)	DOI: 94.6 weeks DUP: 44.0 weeks	<5 weeks	SGA, OM	3 years	82.2	1.5 T/BRAINS2	multiple brain regions	Significant progressive caudate volume increase found in patients compared to controls
Lappin *et al.* 2014	het; n=42/ (27.7 ± 8.8)	n=32/ (29.8±8.6)	Median DUP: 6.7 weeks	unclear	FGA, SGA, OM	6 years	42.5	1.5 T/Longitudinal FreeSurfer (v5.3)	bilateral hippocampi	1. Bilateral hippocampal volume increases were found in 29% of patients, with increased volume associated with a less severe illness course 2. No difference in hippocampal volumes noted between patients and controls
Roiz-Santiánez *et al.* 2015	SCZ; n=109/ (29.44±8.21)	n=76/ (27.80±7.73)	DOI: 94.6 weeks DUP: 44.0 weeks	<5 weeks	SGA, OM	3 years	82.2	1.5 T/BRAINS2	multiple brain regions	At baseline, patients demonstrated cortical thinning in the frontal, temporal, parietal and occipital lobes. Increased cortical thinning globally and in particular in the frontal cortex was demonstrated in the control group over time.
Gutiérrez-Galve *et al.* 2015	het; n=27/ (25.9±6.5)	n=25/ (26.8±7.1)	unclear	≤12 weeks	FGA, SGA	2 years	69.3	1.5T /Longitudinal FreeSurfer version 4.5.0 was used for surface-based morphometric parcellation and estimation of thickness change over time based on the Desikan-Killarney Atlas.	multiple brain regions	Progressive cortical thinning was found in the superior and inferior frontal and, to a lesser extent in the superior temporal cortex in the patient group compared to controls.
Vázquez-Bourgon *et al.* 2016	rs6675281;Leu/leu; n=46 (29.3±7.5) Rs6675281;Phe-Ca; n=17 (32.7±9.7) rs821616;Ser/Ser; n=4 (27.7±2.6) rs821616;Cys-Car; n=56 (29.7±7.9)		DUP: 55.6 weeks DOI: 124.8 weeks DUP: 66.4 weeks DOI: 89.6 weeks DUP: 13.6 weeks DOI: 47.6 weeks DUP: 56.4 weeks DOI: 110.4 weeks	unclear	SGA, OM	3 years	unclear	1.5 T/BRAINS2	multiple brain regions	Patients homozygous for the Leu allele of the rs6675281 SNP had a significant progressive cortical thinning while those carrying the Phe allele presented an increase in thickness. When combining the two SNPs a synergic effect on thickness progression was observed, presenting those patients homozygous for Leu607 +Ser704 a more pronounced cortical thinning.
Haukvik *et al.* 2016	het; n=79/ (27.6±7.7)	n=82/ (29.3±7.2)	DUP: 123 weeks	<52 weeks	FGA, SGA, OM	1 year	58.5	1.5 T/Longitudinal FreeSurfer (v5.3)	multiple brain regions	No significant longitudinal sub/cortical structural changes were found
Bodnar *et al.* 2016	het; Risperidone;	n=44/	DOI: 394.6	< 4 weeks	SGA	1 year	unclear	1.5 T/Longitudinal FreeSurfer	bilateral hippocampi	A significant bilateral hippocampal volume increase in the

	n=24/ (22.50±3.50)	(n.a)	weeks DUP: 18.6 weeks					(v5.3) and MAGeT-Brain (Multiple Automatically Generated Templates) algorithm		aripiprazole group compared to the other treatment groups and healthy controls was demonstrated
	het; Olanzapine; n=12/ (22.30±3.20)		DOI: 200.9 weeks DUP:17.8 weeks							
	het; Aripiprazole; n=13/ (23.30±4.10)		DOI: 207.4 weeks DUP:12.8 weeks							
	het; Refused-Treatment; n=13/ (24.30±3.10)		DOI: 255.3 weeks DUP:20.6 weeks							
Buchy *et al.* 2017*	het; n=128/ (24.2±4.0)		DUP: 49.1 weeks DOI: 306.8 weeks	<4 weeks	FGA, SGA	1 years 2 years	57.0 34.0	1.5T / CIVET (v2.0.0) was used for vertex-based corticometric analysis using the Surf Stat toolbox within MATLAB to assess differences in cortical thickness.	multiple brain regions	A worsening of insight between 1 and 2 years follow-up was associated with cortical thinning in the right dorsal pre-central and postcentral gyri
Buchy *et al.* 2018*	het; n=130/ (24.1±4.1)	n=52/ (24.3±3.4)	DUP: 48.3 weeks DOI: 301.6 weeks							Progressive increase in cortical thickness was found in the precentral gyrus bilaterally, extending to the right premotor cortex and paracentral lobule in patients. In controls, progressive increase in cortical thickness was found in the right posterior cingulate gyrus after one year.
Pawełczyk *et al.* 2018	SCZ; PUFA, n=18/ (23.06 ±4.90)	-	Mean DUP:11.9 weeks	Not stated	FGA, SGA, PUFA	6 months	62.0	1.5T /Longitudinal FreeSurfer (v5.3.0) was used to estimate cortical thickness change over time and expressed as symmetrised percentage change (SPC) at each vertex.	multiple brain regions	The placebo group demonstrated significantly greater cortical thinning in the parieto-occipital cortex of the left hemisphere on the border of Brodmann areas 7 and 19 than the PUFA-treated group.
	SCZ; Placebo, n=11 (22.00±3.77)		**Mean DUP: 9.8 weeks**							
Li *et al.* 2018	SCZ; n=41/ (23.90 ± 7.72)	n=39/ (24.01±8.18)	DOI: 36 weeks	Naïve	SGA	6 weeks	78.8	3 T/Longitudinal FreeSurfer (v6.0)	bilateral hippocampi and subfields	At the whole hippocampus level, there were no significant volume differences found in patients but significant volume reduction of some subfields were observed
Tronchin et al. 2020b	het; n=20/ (28.1±8.1)	n=20/ (30.3±7.6)	DUP:51.6 weeks	<8 weeks	FGA, SGA	3.5 years	86.4	1.5 T/Longitudinal FreeSurfer (v5.3)	Prefrontal cortex	Reduction of total prefrontal cortical thickness over time was strongly correlated with change in negative symptoms.

Table 1 Legend:* two follow-up times; ΦTwo different 1.5T MRI brands and acquisition sequences were used for this study; SCZ = schizophrenia; FEAFF= First-episode Affective; FESCZ= First-episode Schizophrenia; het = heterogenous sample (affective and non-affective); DOI = duration of illness; DUP = duration of untreated psychosis; FGA = first-generation antipsychotics; n.a = not available; SGA = second-generation antipsychotics; OM= other medications (mainly, mood stabilisers and antidepressants); PUFA = n-3 polyunsaturated fatty acids as add-on therapy; Disrupted-in-Schizophrenia 1 (DISC1) gene variant type for SNP rs6675281, and Disrupted-in-Schizophrenia 1 (DISC1) gene variant type for SNP rs821616; ↟ = includes the sample and findings reported in DeLisi et al. 1995; Age = age at baseline.

Table 2: Group comparison of progressive brain change over time

Brain Region	Baseline		Follow-up		Mean Vol. Diff. Over time (mm^3) (95% C.I)	% Vol. Diff. Over time (SD)	Group x Time			Group x Time x Laterality		
	Adjusted Mean Vol. (mm^3) (SE)		Adjusted Mean Vol. (mm^3) (SE)				F (1,51)	p	Hedges' g	F (1,51)	p	Hedges' g
	FEP (n=28)	HC (n=28)	FEP (n=28)	HC (n=28)								
Caudate	8001.04 (172.50)	8218.81 (172.50)	7763.75 (159.74)	8149.83 (159.74)	**-168.31 (-299.57, -37.06)**	**-2.13 (1.51)**	**5.86**	**0.02**	**0.66**	0.23	0.64	0.13
Putamen	12477.22 (222.75)	12391.89 (222.75)	12223.64 (216.12)	12398.61 (216.12)	**-260.30 (-473.66, -46.94)**	**-2.08 (1.47)**	**6.07**	**0.02**	**0.67**	0.03	0.86	0.05
Globus pallidus	3833.15 (85.15)	3993.42 (85.15)	3806.78 (81.17)	4016.26 (81.17)	-49.21 (-136.21, 37.79)	-1.26 (0.89)	1.18	0.28	0.30	0.02	0.89	0.04
Nucleus accumbens	1165.84 (29.75)	1203.34 (29.75)	1160.22 (24.84)	1205.64 (24.84)	-7.92 (-54.88, 39.04)	-0.67 (0.47)	0.11	0.75	0.09	1.00	0.32	0.27
Thalamus	16971.56 (221.22)	17693.80 (221.22)	16499.69 (217.14)	17565.34 (217.14)	**-343.41 (-589.14, -97.68)**	**-3.51 (2.48)**	**6.98**	**0.01**	**0.72**	0.64	0.43	0.22
Hippocampus †	8972.39 (124.01)	9166.01 (124.01)	8866.77 (125.07)	9146.37 (125.07)	-85.98 (-199.41, 27.45)	-0.98 (0.69)	2.06	0.16	0.39	0.01	0.94	0.03
Hippocampus ǂ	5560.83 (112.47)	5724.92 (112.47)	5697.26 (123.55)	5757.06 (123.55)	104.29 (-17.92, 186.49)	1.89 (1.34)	0.53	0.47	0.20	1.18	0.28	0.30
Amygdala	3160.27 (53.46)	3208.51 (53.46)	3205.07 (56.67)	3206.43 (56.67)	46.88 (-10.88,104.64)	1.48 (1.05)	1.81	0.19	0.37	2.58	0.11	0.44
Lateral Ventricle	18694.10 (1436.51)	14128.63 (1436.51)	20140.05 (1563.69)	14607.76 (1563.69)	**966.82 (-39.39, 1973.03)**	**4.34 (3.07)**	**3.37**	**0.07 ϕ**	**0.50**	**4.38**	**0.04**	**0.57**
Third Ventricle	917.33 (63.84)	850.59 (63.84)	973.39 (73.70)	880.15 (73.70)	26.50 (-41.26, 94.26)	2.63 (1.86)	0.54	0.47	0.19	-	-	-
Total White matter	460972.52 (5223.60)	477984.35 (5223.60)	459682.90 (5380.71)	477362.00 (5380.71)	-667.27 (-5 222.46, 3 887.92)	-0.15 (0.11)	0.08	0.78	0.08	-	-	-
Total Grey matter	647495.84 (4723.89)	656765.01 (4723.89)	638932.15 (5151.78)	649329.12 (5151.78)	-1127.80 (-11 314.52, 9 058.92)	-0.19 (0.13)	0.05	0.83	0.06	-	-	-

Table 2 Legend: Age, gender and ICV were included as covariates for all the mean adjustments and analyses; SE= standard error; C.I = confidence interval; % Vol. Diff. = percentage volume difference; calculated as follows: 100 × [(adjusted volume at follow-Up − adjusted volume at baseline)/adjusted volume at baseline] and difference between groups over time is presented; Negative value indicates a % volume decrease over time; The percent volume differences in FEP's and HC's at baseline and follow-Up were selected to estimate the effect size (Hedges' g); **Bold** = significant values and/or large effect sizes (>0.5); p-values presented are uncorrected; ϕ = a trend towards significance; † = Longitudinal FreeSurfer volumes; ǂ = manually segmented volumes. Of note, there was no significant difference in the results with regards to hippocampal volume deficit progression when analysis was repeated using the manual segmentation data.

Table 3: Sociodemographic and clinical characteristics of participants

Variables		**Patients (n=28)**	**Controls (n=28)**	**Comparison (T/χ^2, p)**
Age at baseline MRI, mean (SD), years		28.5 (9.3)	33.5 (8.8)	-2.07, 0.04
Time between Scans, mean (SD), years		3.2 (1.1)	3.2 (0.9)	0.11, 0.91
Years of Education, mean (SD), years		16.0 (2.7)	17.8 (3.0)	-2.37, 0.02
Gender, n (% male)		18 (64.3)	14 (50.0)	1.15, 0.28
Age of onset, mean (SD), years		25.7 (10.1)		
DUP, mean (SD), months		13.9 (16.5)		
TICV, mean (SD), cm^3		1570.5 (132.1)	1548.8 (153.1)	0.60, 0.56
Current Cannabis Users, n (%)	None/Minimal users: Baseline	16 (57.1)	23 (82.1)	4.14, 0.04
	None/Minimal users: Follow-Up	27 (96.4)	28 (100.0)	1.02, 0.31
Antipsychotic Dosage [Total CPZ equiv. (mgs)]†	Daily dose: Baseline[a]	235.5 (198.1)		
	Daily dose: Follow-Up[b]	341.2 (285.9)		
	Cumulative dose: Baseline[c]	6531.1 (8004.9)		
	Cumulative dose: Follow-Up[d]	264912.4 (252121.4)		
Clinical Variables of Patients		**Baseline**	**Follow-Up**	**Comparison (T, p)**
PANSS, mean (SD)	Positive	10.7 (5.2)	3.8 (5)	5.41, p<0.001
	Negative	7.6 (6.0)	4.9 (6.2)	1.92, p = 0.07
	General psychopathology	15.9 (8.0)	7.7 (7.1)	3.89, p<0.001
GAF, mean (SD)		51.3 (11.3)	75.7 (14.8)	-7.87, p<0.001

Table 3 Legend: CPZ= chlorpromazine equivalents; DUP = duration of untreated psychosis; GAF= global assessment of functioning; SD = standard deviation, TICV= Total Intracranial Volume; PANSS= positive and negative syndrome score (0-6 point scale); †= antipsychotic medication was converted to chlorpromazine equivalents (CPZ) [(Lehman *et al.*1998; Taylor *et al.*2007; Woods, 2003)]; [a] Data based on: n=25; [b] Data based on: n=16; [c] Data based on: n=25; [d] Data based on: n = 26.