

# Subcortical Brain Morphology in Schizophrenia

*Descriptive analysis based on MRI findings of subcortical brain  
volumes*

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## 1. Abstract

The aim of this study was to investigate magnetic resonance images (MR) from patients with schizophrenia and healthy control subjects for difference in brain morphology with focus on subcortical brain volumes.

**Method:** The study compared fourteen subcortical brain structure volumes of 96 patients diagnosed with schizophrenia (n=81) or schizoaffective disorder (n=15) with 106 healthy control subjects. Volume measures were obtained using voxel-based morphometry (FreeSurfer software suite) of T1-weighted MR images.

**Results:** When adjusting for intracranial volume, age and gender, the hippocampus volume was smaller both on the right and left side in the patient group ( $p < .001$ ) as compared with healthy controls. Pallidum was found to have an increased volume bilaterally in the patients ( $p < .001$ ), and volume was positively related with disease duration and inversely with age at onset. Caudate and amygdala in the right hemisphere was larger ( $p < .01$ ) and showed trend effects for being larger also in the left hemisphere. There was a trend for a larger right accumbens in the patients.

First generation neuroleptic medication affected basal ganglia volumes differently than second generation neuroleptics with stronger effects on putamen but also on pallidum volume increase.

**Conclusions:** Schizophrenia has brain morphological correlates, and this study confirms that hippocampus is reduced in patients with schizophrenia. This study also presents an interesting subcortical brain region volume difference regarding medication.

### *Keywords*

Schizophrenia, magnetic resonance imaging, voxel-based morphometry, subcortical brain structures, antipsychotic medication.

## **2. Background**

### **2.1 Schizophrenia**

Schizophrenia is a chronic disease affecting about 1 % of the population world-wide (1). The severity may be illustrated by a suicide rate of 10% (1), about 75% of the patients have relapses and continued disability and one out of three fails to respond to standard treatment (2).

#### **2.1.1 Symptoms**

The disease is characterized by fundamental and characteristic alterations of thinking and perception; inappropriate or blunted affects, thought echo, which may have the character of thought insertion or withdrawal, or thought broadcasting, hallucinatory voices commenting or discussing the patient in the third person (3).

The symptoms are often categorized in clusters; positive symptoms, including hallucinations, delusions, thought disorder, and paranoia; cognitive dysfunction, especially in attention, working memory, and executive function; negative symptoms with anhedonia, social withdrawal and thought poverty (4). The symptom clusters do not exclude each other, but they are often present in different degrees across patients.

#### **2.1.2 Etiology and Epidemiology**

The etiology of schizophrenia remains unclear and is considered to be multifactorial. Heritability is estimated to up to 85% (5,6) and supported by increased risk in individuals with a schizophrenic sibling; 8-10%, and a concordance rate of 40-50% among monozygotic twins (4).

This risk pattern is not consistent with heritability as the single cause for schizophrenia (1). Prenatal maternal illnesses during the second trimester and perinatal birth complications have also been found to be predisposing risk factors (4).

Other risk factors include substance use, and traumatic life events (2). Men are more frequently and more severely affected than women (1), with a risk ratio men:women found to be 1.4 (7).

Being born in cities, having moved to a city, social migration and migration in general, as well as being born in winter or spring, have also been found to have a positive correlation with the incidence of schizophrenia (7-9). Paternal age is risk factor of intermediate magnitude (10). It should be noted that such findings do not imply causality, but might be due to a hitherto unknown confounding factor.

### **2.1.3 Treatment**

Antipsychotic pharmaceutical therapy, family interventions, and psychoeducational interventions have shown to be effective in ameliorating symptoms of schizophrenia (2). First-generation antipsychotic agents (FGA), e.g. haloperidol and chlorpromazine, are effective in the treatment of positive psychotic symptoms, but associated with motor side-effects (11,12).

The second-generation antipsychotics (SGA), e.g. risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole are effective and generally better tolerated but, are associated with metabolic side-effects, including weight-gain and increased triglycerides and cholesterol (12,13). Pharmacological treatment has shown good effect on positive symptoms, but no pharmaceutical treatment has been proved to be effective on negative symptoms (11-13).

While FGAs generally act as dopamine D<sub>2</sub>-receptor antagonists (13), many SGAs have a high serotonin 5-HT<sub>2A</sub>-receptor/D<sub>2</sub>-receptor affinity ratio (14). This may be explanatory to the differences in both effects and side-effects seen between the two groups of medication.

## 2.2 Brain structure in schizophrenia

### 2.2.1 Findings from neuroimaging studies

#### *Reduced total brain volume*

The advance of *in vivo* magnetic resonance imaging (MRI) techniques has allowed for an increasingly accurate investigation of brain structures. Although not always reproducible (15), total brain volume is found to be reduced in patients with schizophrenia compared to healthy controls by approximately 2 % (16,17).

#### *Ventricular enlargement*

The most prevalent findings include ventricular enlargement (18,19) and regional volume reduction in the superior temporal gyrus, thalamus, hippocampus, and frontal lobe (18,19). Increased ventricular volume in schizophrenia was shown in early computer tomography (CT) studies (20), and is a consistent finding in schizophrenia (16). A study by Gaser et al. supports the hypothesis that ventricular enlargement is due to focal volume decreases, especially in the thalamus, putamen, and superior temporal gyrus (21).

#### *Reduced fronto-temporal cortical thickness*

Reduced cortical thickness has been found in patients diagnosed with schizophrenia in widespread areas in prefrontal and temporal brain regions, bilaterally (22,23). Reductions in prefrontal cortical white matter volume have been associated with negative symptoms (24).

#### *Impairment of brain circuitry*

Affective and cognitive components of symptom spectrum associated with schizophrenia, such as empathy and executive function, represent higher level brain processes (25). Morphological brain correlates of schizophrenia are thought to implicate a network of frontal, temporal, limbic, striatal, and thalamic regions showing reduced grey matter in patients (26).

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## 2.2.2 Effects of treatment and duration

Medication can affect brain region volumes. In a recent meta-analysis of bipolar disorder, lithium use was associated with increased total gray matter volume (27), for example. Antipsychotic medication has been found to increase basal ganglia volume (28), although this was in a small group of patients (n=29) and healthy controls (n=10). Other studies indicate that this effect is restricted to haloperidol, and not found in subjects who have used second generation antipsychotics (29). In line with the hypothesis that volume change is dependent on the antipsychotic drug administered, a recent study not discriminating FGA and SGA medication found no dosage effect on any subcortical volumes (30). Findings from the same study indicate a correlation between greater volume loss and poor clinical outcome (30).

Age is another factor that is found to strongly correlate with total grey matter volume, as well as specific brain regions (31). The regression slope was also found to be steeper in patients compared to controls, suggesting a progressive loss of grey matter (31,32).

## 2.2.3 Brain imaging methods

### *Voxel-based morphometry (VBM)*

One voxel represents the smallest three-dimensional volume element of an MR-image, thus the size of a voxel depends on the resolution of the MR image, as is the case with a pixel of a two-dimensional image. VBM is an image analysis or image post processing method that calculates the probability of the presence of gray or white matter voxel by voxel (32), also described as the density of gray and white brain matter(33). The method is automated and may calculate brain region volumes of the whole brain(33).

### *Region of interest (ROI) studies*

This method is based on an a priori hypothesis and manual outlining to obtain volume measurement (34). VBM-based methods are automated or semi-automated and allows for measuring several structures simultaneously in the brain, while region-of-interest-

based studies typically measure one structure at a time usually by manual delination which is time-consuming and disadvantageous in the case of large subjects samples.



### **3. Aim**

The aim of this study was to study subcortical volumes in patients diagnosed with schizophrenia compared to healthy controls, and to investigate correlations between volume and medication, duration of illness and age at onset.

#### **3.1 Hypothesis**

The main hypothesis of this study was; subcortical brain volumes in patients diagnosed with schizophrenia differ from healthy controls. Two subsequent hypotheses were formulated; hippocampus volume is decreased, and; basal ganglia volume is correlated to the antipsychotic medication administered.

## 4. Methods

### 4.1 Material

The data in this paper has been obtained as a part of the Human Brain Informatics (HUBIN) project. The project was planned and performed at the Karolinska Institutet and Hospital in Stockholm. All subjects have given their written consent to participate in accordance with the Declaration of Helsinki, the project was approved by the regional and local research ethics committees of the Karolinska Institutet.

#### 4.1.1 Subject description

Patients were included from four psychiatric clinics specialized in the treatment of psychosis in Stockholm County, Sweden, between 1998 and 2003. They were asked to participate in a clinical interview, deliver blood-samples for biochemical and genetic investigation, to undergo an MR investigation of the brain structure, and permission was given to access their medical record. The clinical interview included the Structured Clinical Interview for the DSM-III-R (SCID-I) (36) and patients were classified according to DSM-III-R or DSM-IV diagnostic criteria. Healthy control subjects were recruited from population registers, and among hospital staff and students at the participating centres.

A subpopulation of these patients has been described earlier (37), focusing on caudatus, putamen and nucleus accumbens grey and white matter volumes from manual delineation.

The dataset consisted of 111 patients divided into 6 diagnosis categories and one healthy control group (n=106). Seven patients not categorized by diagnosis were excluded. Eight patients who did not fill the diagnostic criteria (including one subject with confirmed hepatitis C infection) were excluded.

The main calculations will be made merging the schizophrenia (n=81) group and the schizoaffective disorder (n=15) groups, here referred to as the Patient group (n=96).

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Age at onset was defined as onset of psychotic symptoms according to any available source. Duration of illness was defined as the difference in years between age at onset and age at investigation (22).

Local guidelines at Karolinska Institutet made up the basis for calculation of haloperidol equivalent dosage, based on an interview and medical records.

Antipsychotic medication was classified as first-generation, including haloperidol, perfenazine, zuclopenthixole, and fluanxol (n=41) or second-generation, including clozapine, olanzapine, and risperidone (n=44). Three patients received both FGA and SGA medication and 8 patients received no medication. Further description is featured in table 1.

## 4.2 MRI acquisition and post-processing

The same 1.5 Tesla General Electronics Signa scanner system at the MR Research Centre at the Karolinska Institutet was used for examination of all subjects. A three-dimensional spoiled gradient recalled pulse sequence was used for T1-weighted images with the following parameters: 1.5 mm coronal slices, no gap, 35° flip angle, repetition time 24 ms, echo time 6.0 ms, number of excitations 2, field of view 24 cm, acquisition matrix 256 x 192. Data from T1-weighted images were used for image post processing.

### 4.2.1 Image processing

The MRI data represents a three-dimensional matrix of volumetric units, voxels, with registered signal intensity from 0 to 1. The value tends to be closer to either one of these extremes, thus not normally distributed. The MRI smoothing process contributes to normalizing the data, as well as allowing segmentation at higher resolution than the original MRI data, by averaging nearby located voxels (33).

### 4.2.2 Freesurfer segmentation

The FreeSurfer segmentation procedure automatically identifies volumes of subcortical structures (32,38). The algorithm labels each voxel as one of 40 brain

structures (38). A reliability study has also been conducted to validate the software used in this study, where five experts independently labelled subcortical regions manually. The calculated volumes were then compared to the volumes calculated on the basis of automatically labelled volumes, resulting in statistically indistinguishable results (32).

### 4.3 Statistical analysis

#### *Software*

Automatic subcortical labelling and volume measurements were performed with FreeSurfer version 2.2.3 running on an Apache Linux system. The FreeSurfer image analysis suite is freely available (39). SPSS version 16 for Windows was used for statistical analyses. Microsoft Excel was used for data analysis and graphical presentation.

#### *The studied brain volumes*

The FreeSurfer software calculates a wide array of data from the entire brain, including 40 defined subcortical volumes. The automatically delineated volumes studied include thalamus, caudate, putamen, pallidum, hippocampus, amygdala and accumbens. All subcortical volumes are presented as absolute volumes ( $\text{mm}^3$ ). This is a more direct approach than to study volumes relative to total intracranial volume, although often performed (16,17,40,41). To correct for individual variance in head size, intracranial volume (ICV) was added as a covariate in the statistical analyses.

#### *Statistical methods applied*

The normality of subcortical volume distributions within the patient and control groups were investigated by visual inspection of residuals of all groups studied.

Student's T-test was used to investigate differences in descriptive variables across all groups studied. Except for administered haloperidol equivalents, no difference was found. Patients receiving SGA had a higher daily haloperidol equivalent dosage compared to patients receiving FGA, 5.6 and 2.7 mgeqv/daily, respectively.

Mean volumes were compared across subject groups, including ICV as a covariate in an analysis of covariance (ANCOVA). To validate the findings, age and gender were then added as covariates as well. Comparing across subgroups defined by the medication they used, required three statistical tests. A Bonferroni test with alpha level adjusted to 0.016 was used to correct for multiple comparisons.

To investigate the effect of medication, age at onset of illness and duration of illness, partial correlation coefficients were computed when controlling for age, gender and ICV. Medication was investigated in terms of haloperidol equivalents and a dichotomous classification as FGA or SGA.

As a basis for performing these tests, normality of distribution, correlations amongst covariates, linearity, and homogeneity were investigated to make sure the data have the distribution required for the tests to be valid.

As mentioned above, gender was added as a covariate in an ANCOVA model, thus operating with dichotomous data in a model which requires normally distributed data.

## 5. Results

No significant differences in age or gender distribution were found between the control and patient groups. As shown in Table 2, the volume of the hippocampus on both sides was found to be highly significantly smaller in the patient group. Pallidum on both sides were found to be larger in the patient group. As noted in Figure 5, all p-values were  $<.001$ , also when adjusting for age and gender. In this study, no significant difference in total intracranial volume was found.

Right caudate and right amygdala were significantly larger and smaller volumes, respectively, in the patient group compared to healthy controls,  $F=7.2$ ,  $p=.008$  and  $F=7.5$ ,  $p=.007$  respectively.

### *Trends*

There were trends for caudate and amygdala on the left side ( $F=5$ ,  $p=.03$  for both structures). Table 2 and figure 5 clearly shows that the differences are in the same direction bilaterally, supporting the consistency of this finding within this material.

### *Effects of disease duration and medication at MRI*

A positive correlation between volume of pallidum and duration of illness and a negative correlation with age at onset, controlling for age, gender and ICV, was found (correlation coefficient 0.3,  $p<.01$  for both tests). Details are presented in Table 3.

No significant correlation between the subcortical volumes and administered haloperidol dosage at time of MRI was found in the patient group.

### *FGA vs SGA medication*

A subgroup ( $n=85$ ) within the patient group receiving either FGA ( $n=41$ ) or SGA ( $n=44$ ) medication was studied, thereby excluding patients receiving both and no medication. Comparisons were done on volumes adjusted for age, gender and ICV. Putamen volume in patients receiving FGA was larger as compared to both SGA and healthy controls. Caudate volume was larger in the FGA group compared to healthy controls, no significant difference was found between FGA and SGA groups.

Pallidum volume was larger in the FGA group compared to healthy controls bilaterally. Left pallidum was larger in SGA compared to healthy controls, whereas right pallidum in SGA was smaller than FGA. Hippocampus volume in both FGA and SGA groups were smaller than in healthy controls. Patients receiving first-generation antipsychotic (FGA) medication were found to have a larger pallidum volume compared to patients receiving second-generation antipsychotic (SGA).

All results are presented in table 4 and figure 7.

## 6. Discussion

The hippocampus volume was significantly smaller in patients compared to healthy controls. The absence of difference in patients receiving FGA or SGA suggests this effect is due to the disease, rather than medication.

Putamen volume bilaterally and the right pallidum volume were larger in patients receiving FGA compared to both SGA and healthy control groups. As no significant difference between patients receiving SGA and healthy control subjects was found, this suggests that the volume increase is due to the FGA medication. Left, but not right, pallidum was found to be significantly larger in patients receiving SGA compared to healthy controls as well, making it less likely that pallidum volume difference is a medication effect.

The main hypothesis that subcortical brain volumes in patients diagnosed with schizophrenia differ from healthy controls was supported by the findings of this study. Findings from both the correlation analysis (Table 3) and group-wise comparison by medication (Table 4) support the hypothesis that basal ganglia volume is correlated to the class of antipsychotic medication administered. No dosage-effect of medication on subcortical volumes was found in this study but measures were only obtained from one occasion (at MRI examination).

### *Intracranial volume*

This material showed no significant difference in ICV between the two groups. This is in line with the more recent inconsistency of this finding (15).

### *Subcortical volume differences*

In this study, we found reduced volumes of left and right hippocampus in the patients as compared to healthy subjects. Reduced hippocampal volume in patients diagnosed with schizophrenia has also been found previously (16). This finding is considered to be a consistent finding in schizophrenia (19).



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Previous studies have found an increase in caudate, putamen and pallidum volumes in chronic schizophrenic patients (42), concordant with the findings of this study.

### *Medication dosage*

Medication effects, associated with brain region volume enlargement (43), may have been a contributing factor to the previously reported larger pallidum volume in patients (44). The group difference found in this material, with larger putamen and right pallidum volumes in patients receiving FGAs compared to SGA, suggests that this may partly be due to the medication. As this is a cross-sectional study, conclusions cannot be drawn, but the findings do point out a potential direction for further investigation. This hypothesis could be tested in a follow-up study of this cohort.

The calculation of haloperidol equivalent dosage is not at all straight-forward for antipsychotic drugs, and may be contributing to the difference in administered haloperidol equivalents found when comparing FGA and SGA. The pharmacological differences between FGA and SGA, as well as different molecular targets of action within the groups, complicate the matter. These problems of the calculation of haloperidol equivalent dosage suggest further studies to focus on individual antipsychotic drugs. Such a circumvention of this problem may require larger sample sizes to achieve adequate group sizes as the number of administered drugs increases.

This data do not provide retrospective data on medication dosage. Dosage is titrated individually by symptom relief; a high dosage could be due to severity of symptoms as well as individual variations in pharmacokinetics, distribution and metabolism. As a result, this null finding does not imply that medication dosage is without effect of brain region volumes.

### *FGA and SGAs*

The mechanism of antipsychotic drugs on brain volume remains uncertain. One hypothesis to explain the volumetric differences in the basal ganglia is that chronic D<sub>2</sub>-receptor antagonist influence leads to a receptor proliferation, which in turn leads

to increased metabolism, blood flow and size (45). SGA, having different receptor affinity, have been found to ameliorate this effect (45).

With the exception of hippocampus and left pallidum, FGA had larger and SGA had smaller subcortical brain region volumes compared to healthy controls. This is in line with the trends of a recent review by Scherk and Falkai (45).

Emerging evidence support a substantial diversity of antipsychotic drugs, also within the groups of FGA and SGA (46). As the choice and combinations of drugs vary in clinical practise, an observational setting as this study requires some level of grouping in order to achieve an adequate power of the statistical analysis. Hence, the traditional classification of drugs as either FGA or SGA was chosen.

The strengths of this study include a fairly large sample size and reproduction of previous findings.

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## 9. Appendix

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Table 1 Descriptive variables

	Patients (n=96)			Control (n=106)		
	Mean	Std. Dev.	Range	Mean	Std. Dev.	Range
Age	42.1	7.31	(25 - 57)	41.5	9.01	(19 - 56)
Gender [male-female]	[70 - 26]			[72 - 34]		
Age at onset, years <sup>a</sup>	24.6	5.89	(14 - 45)			
Duration, years <sup>a</sup>	17.3	8.62	(0.4 - 41.1)			
Medication Dosage <sup>b</sup>	3.97	3.28	(0 - 16)			
ICV <sup>c</sup>	1735	286	(1301 - 2420)	1722	300	(1275 - 2599)
Antipsychotic medication (N)						
None	8					
First-generation	41					
Second-generation	44					
Both	3					

a. Data available for 94 patients

b. Dosage converted to Haloperidol-equivalents, mg/day

c. Volume  $10^3 \text{ mm}^3$

Table 2 Differences in subcortical volume measures between patients (n=96) and controls (n=106), adjusted for ICV, age and gender.

	Patients		Controls		Adjusted for age, gender and ICV		
	Mean <sup>a</sup>	Std. Error	Mean <sup>a</sup>	Std. Error	F	p	Eta sq <sup>b</sup>
Left thalamus	7589.8	86.85	7687.5	82.65	1.75	0.187	0.01
Right thalamus	7849.3	87.89	7797.8	83.64	0.02	0.877	0.00
Left caudate	3821.6	49.40	3669.7	47.01	5.05	<b>0.026</b>	0.02
Right caudate	3847.6	49.02	3667.7	46.65	7.18	<b>0.008</b>	0.04
Left putamen	5593.4	62.50	5420.3	59.48	4.08	<b>0.045</b>	0.02
Right putamen	5548.4	64.15	5341.2	61.05	5.69	<b>0.018</b>	0.03
Left pallidum	2025.2	25.50	1865.2	24.26	24.92	<b>&lt; 0.001</b>	0.11
Right pallidum	1945.4	26.20	1811.4	24.93	15.44	<b>&lt; 0.001</b>	0.07
Left hippocampus	4126.9	45.29	4354.5	43.1	17.58	<b>&lt; 0.001</b>	0.08
Right hippocampus	4336.9	43.48	4536.5	41.38	14.77	<b>&lt; 0.001</b>	0.07
Left amygdala	1709.7	23.03	1760.8	21.92	5.02	<b>0.026</b>	0.02
Right amygdala	1677.9	21.08	1738.9	20.06	7.51	<b>0.007</b>	0.04
Left accumbens	547.7	9.93	556.6	9.45	0.63	0.428	0.00
Right accumbens	558.4	9.42	585.1	8.96	5.30	<b>0.022</b>	0.03

a. Raw volume  $\text{mm}^3$

b. Partial eta squared

*Table 3 Correlations between subcortical volumes and medication dosage, disease duration and age at onset at MRI in the patient group, adjusted for age, gender and ICV*

	Dosage <sup>a</sup> (df=91)		Duration (df=89)		Age at onset (df=89)	
	corr <sup>c</sup>	p	corr <sup>c</sup>	p	corr <sup>c</sup>	p
Left thalamus	-0.051	0.625	0.175	0.097	-0.146	0.167
Right thalamus	-0.091	0.387	0.202	0.055	-0.185	0.080
Left caudate	-0.089	0.396	0.182	0.084	-0.162	0.124
Right caudate	-0.093	0.378	0.197	0.061	-0.180	0.088
Left putamen	-0.069	0.513	0.158	0.134	-0.145	0.171
Right putamen	-0.107	0.308	0.166	0.116	-0.162	0.126
Left pallidum	-0.054	0.609	0.336	<b>0.001</b>	-0.308	<b>0.003</b>
Right pallidum	-0.040	0.701	0.343	<b>0.001</b>	-0.318	<b>0.002</b>
Left hippocampus	-0.123	0.239	0.127	0.229	-0.143	0.178
Right hippocampus	-0.080	0.449	0.049	0.643	-0.070	0.510
Left amygdala	-0.075	0.472	-0.019	0.862	0.002	0.984
Right amygdala	-0.063	0.548	0.056	0.600	-0.051	0.633
Left accumbens	-0.197	0.058	0.109	0.306	-0.090	0.394
Right accumbens	-0.150	0.153	0.070	0.507	-0.077	0.471

- a. Neuroleptika-equivavelents, Haloperidol mg/day
- b. Antipsychotic medication, FGA and SGA coded as 1 and 2, respectively
- c. Correlation coefficient

*Table 4 Comparison of subcortical volumes between a subgroup of patients (n=85) who received either FGA or SGA medication and healthy controls, calculated with ICV, age, and gender as covariates*

	FGA (n=41) <sup>a</sup>		SGA (n=44) <sup>a</sup>		CTR (n=106) <sup>a</sup>		p <sup>b</sup>		
	Mean	Std. Error	Mean	Std. Error	Mean	Std. Error	FGA vs. SGA	FGA vs. CTR <sub>c</sub>	SGA vs. CTR <sub>c</sub>
Left thalamus	7697	872.0	7556	806.4	7688	879.4	0.345	0.841	0.177
Right thalamus	7983	823.1	7776	845.6	7798	897.5	0.213	0.274	0.700
Left caudate	3904	481.3	3749	430.5	3670	514.4	0.120	<b>0.008</b>	0.398
Right caudate	3956	461.9	3755	451.0	3668	500.4	0.045	<b>0.001</b>	0.333
Left putamen	5783	537.4	5470	664.8	5420	587.4	<b>0.008</b>	<b>&gt;0.001</b>	0.706
Right putamen	5736	588.1	5404	676.9	5341	597.8	<b>0.006</b>	<b>&gt;0.001</b>	0.618
Left pallidum	2094	257.1	1981	226.6	1865	245.4	<b>0.016</b>	<b>&gt;0.001</b>	<b>0.004</b>
Right pallidum	2020	252.5	1890	248.2	1811	258.9	<b>0.010</b>	<b>&gt;0.001</b>	0.070
Left hippocampus	4189	575.2	4043	354.5	4355	398.2	0.119	<b>0.014</b>	<b>&gt;0.001</b>
Right hippocampus	4366	481.6	4272	399.7	4537	418.7	0.340	<b>0.011</b>	<b>&gt;0.001</b>
Left amygdala	1755	229.2	1663	200.7	1761	234.6	0.067	0.553	<b>0.005</b>
Right amygdala	1704	232.8	1646	201.4	1739	203.6	0.245	0.154	<b>0.004</b>
Left accumbens	566	83.5	533	109.8	557	93.1	0.122	0.662	0.153
Right accumbens	579	83.3	541	91.3	585	90.2	0.036	0.639	<b>0.003</b>

a. Raw mean volumes (mm<sup>3</sup>)

b. Based on estimated marginal means controlling for ICV, age and gender  
P-values less than the Bonferroni adjusted alpha level (0.016) are in bold

## 9.2 Figures

Figure 5 Significant volume differences

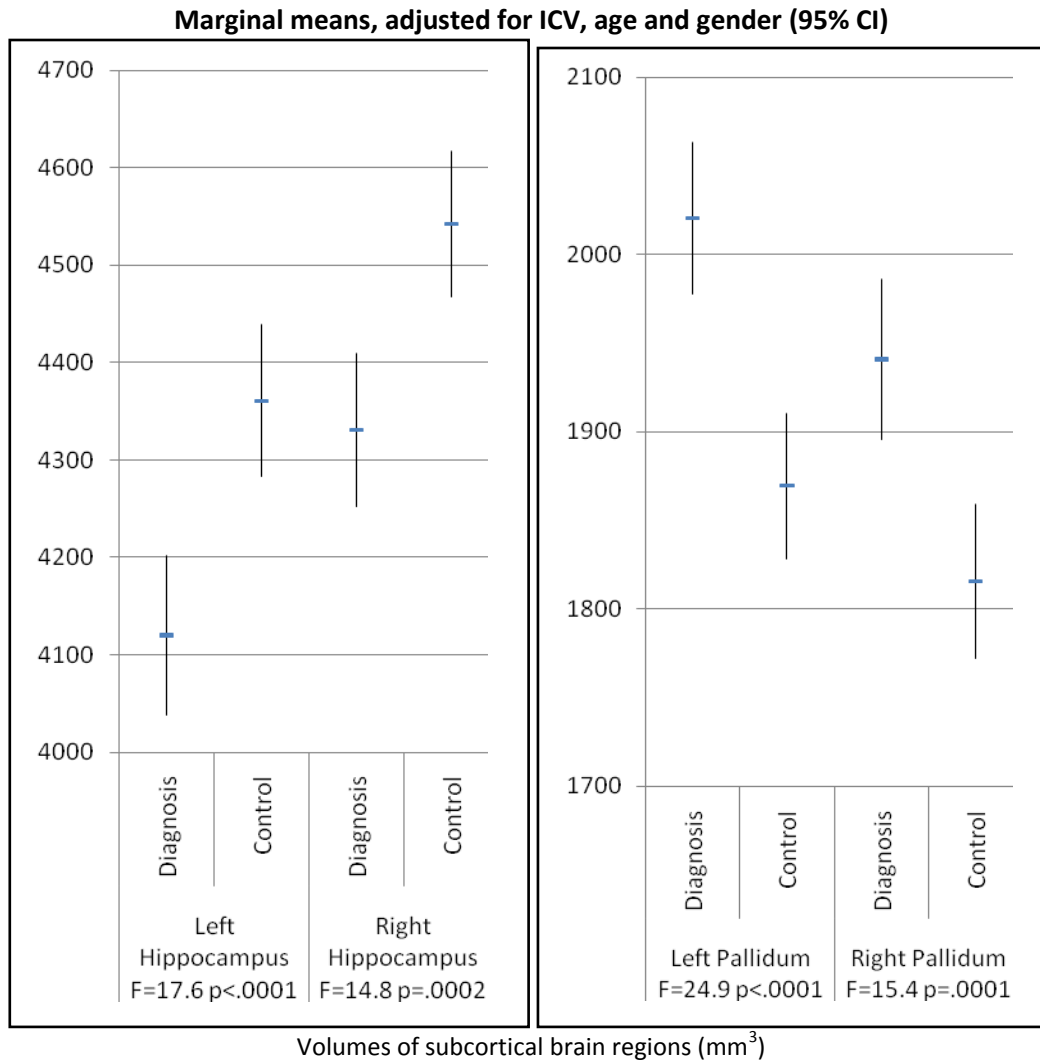
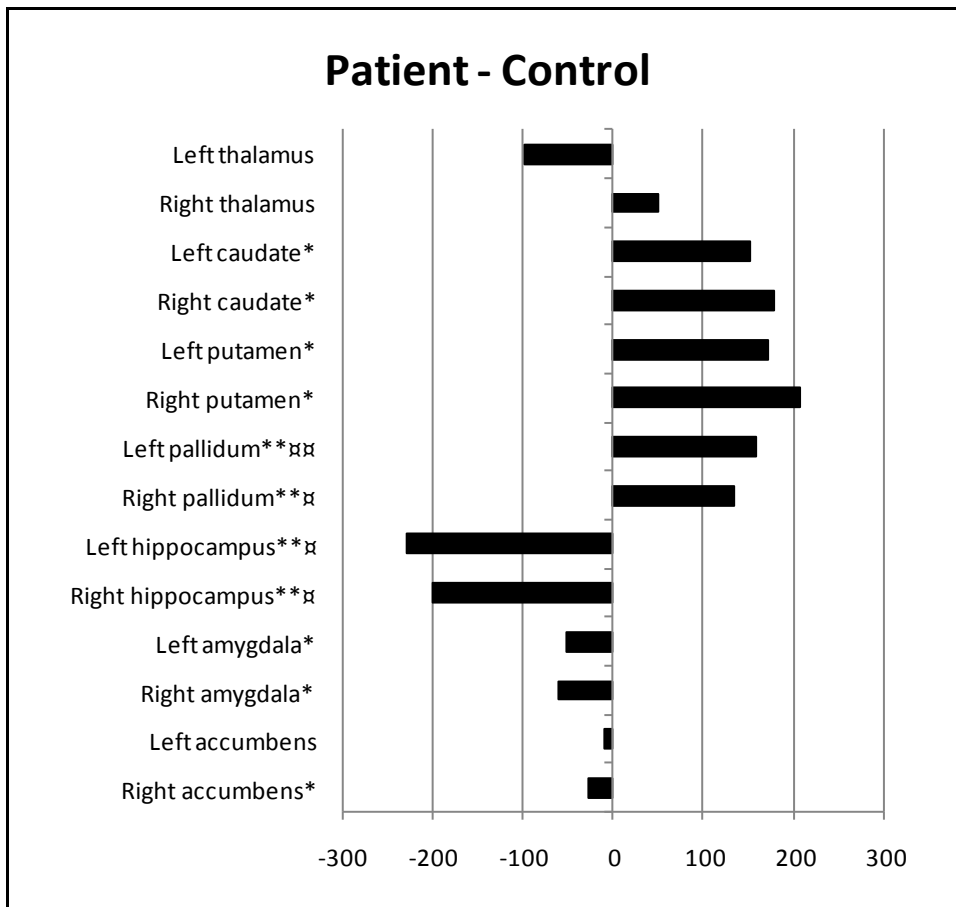


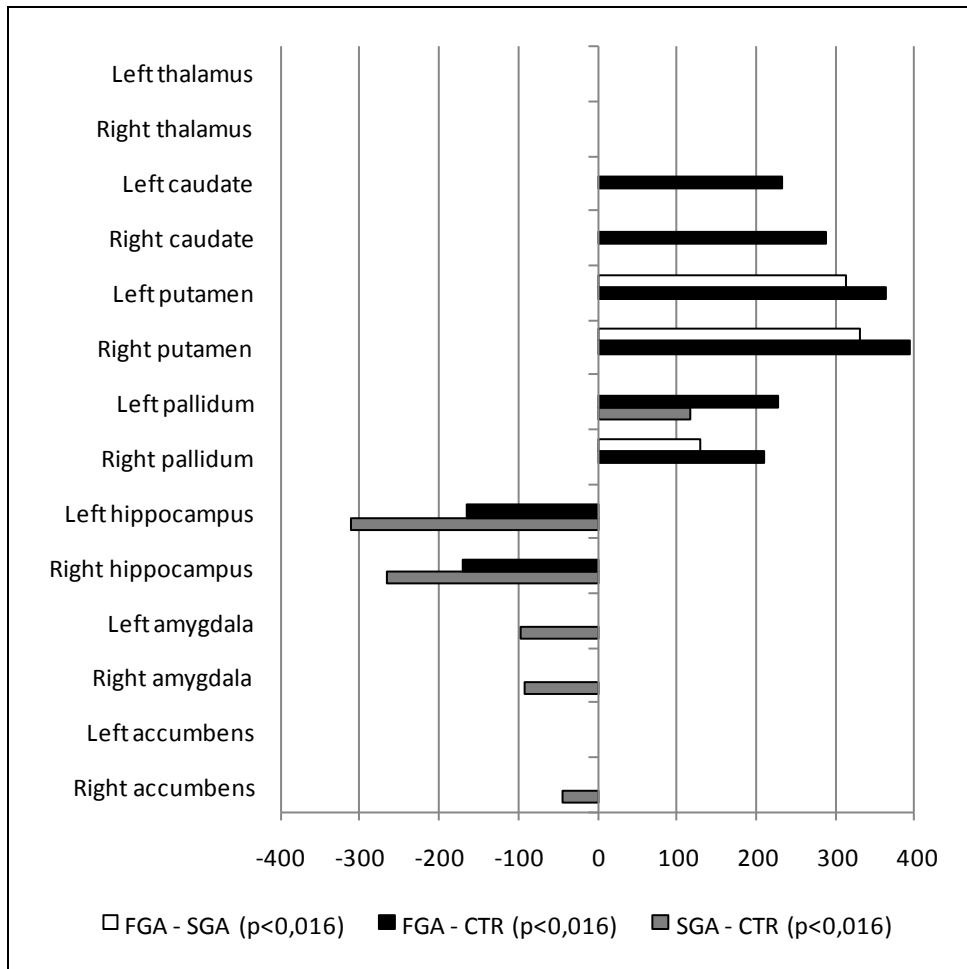
Figure 6 Estimated marginal mean difference, patients - controls



Legend: \*:  $p < 0,05$ , \*\*:  $p < 0,001$ , ⌘:  $F > 10$ , ⌘⌘:  $F > 20$

Crude difference of raw volumes ( $\text{mm}^3$ ). F and p are calculated based on estimated marginal means adjusting for age, gender and ICV.

Figure 7 Summary of significant differences; FGA vs. SGA vs. CTR, extracted from table 4



Comparison of raw volumes (mm<sup>3</sup>), p-values based on estimated means adjusted for ICV, age and gender. Bonferroni adjusted alpha level 0.016.