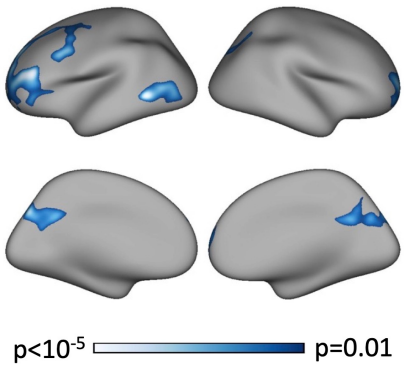
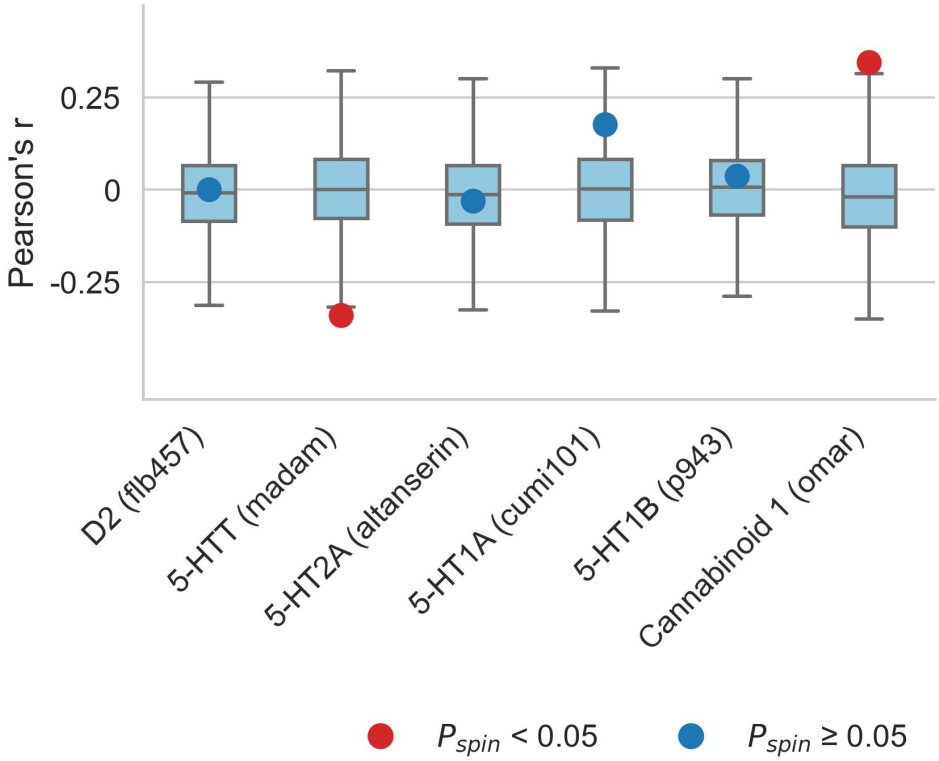
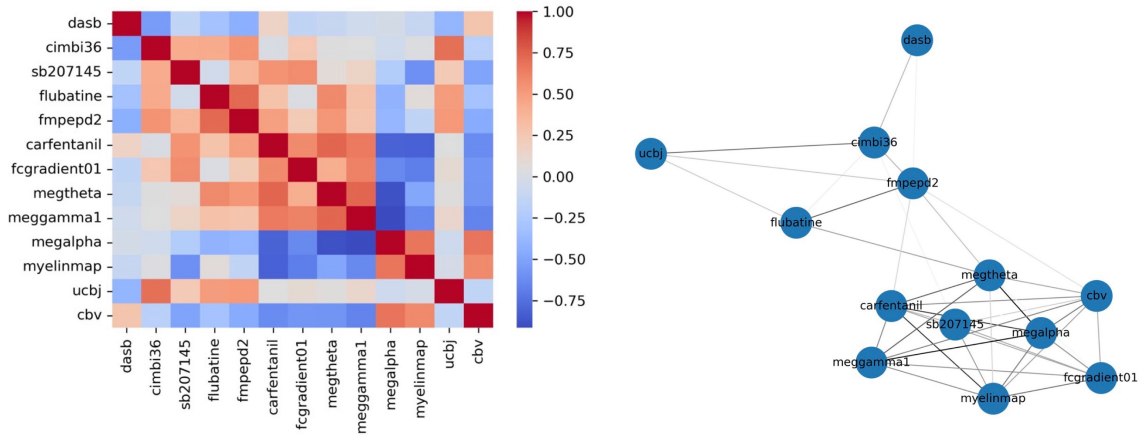
Supplementary figures and tables for Tuominen et al., Molecular, physiological and functional features underlying cortical thinning related to antipsychotic medication use



Supplementary Figure 1 Association between lifetime antipsychotic exposure and cortical thickness thresholded at p=0.01. Model includes age, sex, and diagnostic group as nuisance variables. Colorbar indicates p-value. Results are permutation corrected for multiple comparisons.



Supplementary Figure 2 Antipsychotic sensitivity and brain organization with additional measures. Six features of brain organization were measured with more than one tracer. For the sake of completeness, these measures were also correlated with AP effects on cortical thickness in the Turku sample. In line with the analysis using the primary measures for these features, no statistically significant associations were found.



Supplementary Figure 3 Correlations between features of the brain that are associated with antipsychotic related cortical thinning. Left panel show correlation matrix, colorbar indicates Pearson correlation coefficient r. Right panel shows a spring-embedded representation of the correlations. Topographies of serotonin transporter, synaptic density, 5-HT2A, CB1, and $\alpha 4\beta 2^*$ receptors appear clustered, another cluster is formed by functional measures, cortical myelin, cerebral blood flow, μ- opioid and 5-HT4 receptors.

Supplementary table 1 Sensitivity analyses. The table shows the estimate, standard error, t-value and p-value of antipsychotic exposure on average cortical thickness when including one of the covariates at a time in the model.

Covariate	Estimate	Std. Error	t-value	p-value
Total symptoms score	-1.2E-06	2.5E-07	-4.77	0.0000053
Positive symptoms score	-1.2E-06	2.6E-07	-4.60	0.0000106
Negative symptoms score	-1.2E-06	2.5E-07	-4.86	0.0000036
BMI	-1.1E-06	2.5E-07	-4.30	0.0000347
Hospital days	-1.0E-06	3.1E-07	-3.31	0.0012269
Times admitted	-1.1E-06	2.8E-07	-3.72	0.0003040
GAF	-1.2E-06	2.8E-07	-4.12	0.0000688
SOFAS	-1.2E-06	2.8E-07	-4.19	0.0000532

Supplementary table 2 shows correlations between antipsychotic related cortical thinning and normative features of the brain in the discovery sample (same data as in figure 2)

tracer / measure	class	target	rho	pspin	fdr_corrected_p_value
sch23390	dopamine	D1	-0.13611309816019400	0.2522747725227480	0.3128207179282070
fallypride	dopamine	D2	-0.15145839192235800	0.1648835116488350	0.21297453587974500
dasb	serotonin	5-HTT	-0.4041914204738630	0.0017998200179982	0.007970631508277740
way100635	serotonin	5-HT1A	-0.2230886044601000	0.06729327067293270	0.1097942837295220
az10419369	serotonin	5-HT1B	0.19896995442264000	0.1095890410958900	0.1477069684335910
cimbi36	serotonin	5-HT2A	0.377865933841217	0.0011998800119988000	0.007439256074392560
sb207145	serotonin	5-HT4	0.27514812603014100	0.018998100189981000	0.0368088191180882
gsk215083	serotonin	5-HT6	0.06486864703669620	0.593040695930407	0.6339400542704350
feobv	acetylcholine	vAChT	-0.321011588836917	0.006299370062993700	0.017752770177527700
flubatine	acetylcholine	alpha4 beta2*	0.3662865373866890	0.004899510048995100	0.015498450154984500
lsn3172176	acetylcholine	M1	0.18914965240899800	0.0948905109489051	0.1394860513948610
abp688	various	mGluR5	0.11861066017734100	0.32836716328367200	0.3915146946843780
fmpepd2	various	Cannabinoid 1	0.45584978842246300	0.000999900009999	0.007439256074392560
gsk189254	various	Histamine 3	0.07465882818090720	0.5506449355064490	0.6096426071678550
carfentanil	opioid	mu-opiod	0.308922119988958	0.014698530146985300	0.030376962303769600
ly2795050	opioid	kappa-opioid	0.20964293008754100	0.098990100989901	0.1394860513948610
fcgradient01	functional	Functional Gradient	0.4736608549761900	9.99900009999E-05	0.0030996900309969000
megalpha	functional	Alpha Power	-0.39369935598264800	0.0016998300169983000	0.007970631508277740
megbeta	functional	Beta Power	0.21379662504879700	0.0842915708429157	0.13065193480651900
megdelta	functional	Delta Power	0.28439367925684500	0.014298570142985700	0.030376962303769600
meggamma1	functional	Low Gamma Power	0.4230748599315880	0.0005999400059994000	0.007439256074392560
meggamma2	functional	High Gamma Power	0.25983323129290300	0.0212978702129787	0.0388372927413141
megtheta	functional	Theta Power	0.3769190538769740	0.004999500049995000	0.015498450154984500
megtimescale	functional	Intrinsic Timescale	0.3007630887583380	0.008599140085991400	0.022214445222144500
ucbj	structural	Synaptic Vesicles	0.30075589867662100	0.009499050094990500	0.02265158099574660
cortical thickness	structural	Cortical Thickness	0.09457914724924790	0.42295770422957700	0.48561810485618100
myelin	structural	T1/T2	-0.34840135738894000	0.0038996100389961000	0.01511098890110990
cbf	metabolic	CBF	0.009795333069901100	0.9342065793420660	0.9342065793420660
cbv	metabolic	CBV	-0.37187655201844700	0.0011998800119988000	0.007439256074392560
cmr02	metabolic	CMRO2	-0.014991231074433000	0.9032096790320970	0.9333166683331670
cmrglc	metabolic	CMRGlu	0.26999789426642900	0.022897710228977100	0.039434945394349500

Supplementary table 3 shows correlations between antipsychotic related cortical thinning and alternative tracers (same data as in supplementary figure 3)

tracer	class	target	rho	pspin
flb457	dopamine	D2	-5.79697230025378E-05	0.9996000399960000
madam	serotonin	5-HTT	-0.34088637208110100	0.0040995900409959
cumi101	serotonin	5-HT1A	-0.031009435680068000	0.7922207779222080
p943	serotonin	5-HT1B	0.17632035708924800	0.138986101389861
altanserin	serotonin	5-HT2A	0.036385225482637400	0.7381261873812620
omar	various	Cannabinoid 1	0.34450355205267800	0.005099490050994900

Supplementary table 4 shows correlations between antipsychotic related cortical thinning and normative features of the brain in the replication sample (same data as in figure 4)

tracer / measure	class	target	rho	pspin	fdr_corrected_p_value
dasb	serotonin	5-HTT	-0.42730137785045700	0.00039996000399960000	0.0035996400359964000
cimbi36	serotonin	5-HT2A	0.44723884247094900	0.00029997000299970000	0.0035996400359964000
sb207145	serotonin	5-HT4	0.4685705038863450	0.0010998900109989000	0.004949505049495050
flubatine	acetylcholine	alpha4 beta2*	0.361200659937138	0.0028997100289971	0.007456397217421110
feobv	acetylcholine	vAChT	-0.18615621847142200	0.12138786121387900	0.13892360763923600
fmpepd2	various	Cannabinoid 1	0.5468469740436400	0.0005999400059994000	0.0035996400359964000
carfentanil	various	μ-opiod	0.38768215355838800	0.0025997400259974	0.007456397217421110
fcgradient01	functional	Functional Gradient	0.3648219948521910	0.0061993800619938000	0.012398760123987600
megtimescale	functional	Intrinsic Timescale	0.17808098151252700	0.16498350164983500	0.16498350164983500
megtheta	functional	Theta Power	0.3962061791475740	0.0016998300169983000	0.006119388061193880
meggamma2	functional	High Gamma Power	0.19868373094673000	0.12348765123487700	0.13892360763923600
meggamma1	functional	Low Gamma Power	0.2956246730624560	0.0188981101889811	0.028347165283471700
megdelta	functional	Delta Power	0.22859793901970000	0.0822917708229177	0.10580370534375100
megalpha	functional	Alpha Power	-0.35220229889986500	0.0053994600539946000	0.012148785121487900
myelin	structural	T1/T2	-0.2702431372254100	0.033996600339966	0.047072215855337500
ucbj	structural	Synaptic Vesicles	0.3068443681943620	0.0091990800919908	0.015053040150530400
cbv	metabolic	CBV	-0.3566093662360660	0.007799220077992200	0.014038596140386000
cmruglu	metabolic	CMRGlu	0.15876486313861500	0.1643835616438360	0.16498350164983500

Supplementary table 5 shows all the antipsychotic medications that were used in the Turku sample and a number of patients that were ever exposed to these antipsychotics.

	FEP	CHR
Second generation antipsychotics		
risperidone (n)	50	12
quetiapine (n)	35	13
olanzapine (n)	31	7
aripiprazole (n)	12	3
paliperidone (n)	5	0
asenapine (n)	4	0
ziprasidone (n)	1	0
sulpride (n)	1	0
First generation antipsychotics		
perphenazine (n)	6	2
haloperidol (n)	3	2
flupentixol (n)	2	0
levomepromazine (n)	2	0

Supplementary table 6 shows measures of normative structural and functional features of the cortex used in this study.
For more details please see:
https://docs.google.com/spreadsheets/d/1oZecOsvtQEh5pQkIf8cB6CyhPKVrQuko/edit#gid=1162991686

	Author/Dataset	Year	Tracer / Measure	Target	Reference
0	Jaworska	2020	fallypride	D2	Jaworska et al., 2020, Neuropsychopharm
1	Kaller	2017	sch23390	D1	Kaller et al., 2017, Eur J Nucl Med Mol Imaging
2	Radnakrishnan	2018	gsk215083	5-HT6	Radhakrishnan et al., 2018, J Nucl Med
3	Beliveau	2017	cimbi36	5-HT2A	Beliveau et al., 2017, J Neurosci
4	Savli	2012	way100635	5-HT1A	Savli et al., 2012, Neuroimage
5	Beliveau	2017	az10419369	5-HT1B	Beliveau et al., 2017, J Neurosci
6	Beliveau	2017	sb207145	5-HT4	Beliveau et al., 2017, J Neurosci
7	Fazio	2016	madam	5-HTT	Fazio et al., 2016, Neuroimage
8	Tuominen	NA	feobv	vAChT	NA
9	Hillmer	2016	flubatine	alpha4 beta2*	Hillmer et al., 2016, Neuroimage
10	Naganawa	2020	lsn3172176	M1	Naganawa et al., 2020, J Nucl Med
11	Margulies	2016	fcgradient01	Functional Gradient	Margulies et al., 2016, PNAS
13	Hcps	2022	megalpha	Alpha Power	Shafiei et al., 2022, Plos Biology
14	Hcps	2022	megdelta	Delta Power	Shafiei et al., 2022, Plos Biology
15	Hcps	2022	megbeta	Beta Power	Shafiei et al., 2022, Plos Biology
16	Hcps	2022	meggamma1	Low Gamma Power	Shafiei et al., 2022, Plos Biology
17	Hcps	2022	meggamma2	High Gamma Power	Shafiei et al., 2022, Plos Biology
18	Hcps	2022	megtheta	Theta Power	Shafiei et al., 2022, Plos Biology
19	Hcps	2022	megtimescale	Intrinsic Timescale	Shafiei et al., 2022, Plos Biology
20	Finnema	2016	ucbj	Synaptic Vesicles	Finnema et al., 2018, J Cereb Blood Flow Metab
21	Hcps	2016	thickness	Cortical Thickness	Glasser et al., 2016, Nature
22	Hcps	2016	myelin	T1/T2	Glasser et al., 2016, Nature
23	Dukart	2018	flumazenil	$GABA_A$	Dukart et al., 2018, Sci Rep
24	Dubois	2015	abp688	mGluR5	Dubois et al., 2016, Eur J Nucl Med Mol Imaging
25	Laurikainen	2018	fmpepd2	Cannabinoid 1	Laurikainen et al., 2019, Neuroimage
26	Vijay	2018	ly2795050	kappa-opioid	Vijay et al., 2018, Neuropsychopharmacology
27	Kantonen	2020	carfentanil	mu-opiod	Kantonen et al., 2020, Neuroimage
28	Gallezot	2017	gsk189254	Histamine 3	Gallezot et al., 2010, J Cereb Blood Flow Metab
29	Raichle	NA	cbf	CBF	Vaishnavi et al., 2010, PNAS
30	Raichle	NA	cbv	CBV	Vaishnavi et al., 2010, PNAS
31	Raichle	NA	cmr02	$CMRO_2$	Vaishnavi et al., 2010, PNAS
32	Raichle	NA	cmruglu	CMRGlu	Vaishnavi et al., 2010, PNAS