

Supplementary material to the article “No association between cortical dopamine D2-receptor availability and cognition in anti-psychotic naïve first episode psychosis”

Supplementary Table 1:

Previous studies of cognitive ability and its relationship to dopamine D2-R in healthy controls and in schizophrenia patients. All results listed reflect the relationship between better performance and higher BP_{ND} levels, if error measures were used the correlation has been reversed

Supplementary Table 1

	Population	Ligand	Region	Cognitive function	Relation to D2-R levels
Rao, 2018	13 SCZ (5 anti-psychotic naïve/8 drug free) + 14 HC	[¹¹ C]FLB 457	DLPFC	Verbal learning and memory	SCZ: 0 HC: -
			DLPFC	Language/speed of processing	SCZ: - HC: 0
Vyas, 2018	25 SCZ (20 anti-psychotic naïve/5 drug free) + 19 HC	¹⁸ F-fallypride	DLPFC, PFC, hippocampus, thalamus	Verbal learning and memory	SCZ: - HC: 0
			Dorsal striatum, thalamus, limbic	Executive function	SCZ: - HC: +
Slifstein, 2015	20 SCZ (6 anti-psychotic naïve/14 drug free) + 21 HC	[¹¹ C]FLB 457	DLPFC	Working memory	SCZ: 0 HC: +
Fagerlund, 2013	24 FEP anti-psychotic naïve + 20 HC	SPECT [¹²³ I]epidepride	Frontal cortex	Executive function (set-shifting) Executive function (planning) Attention	SCZ: + HC: ∪ SCZ: ∩ HC: ∩ SCZ: ∩ HC: ∪
Lumme, 2010	40 HC	[¹¹ C]FLB 457	ACC, PFC, hippocampus amygdala etc.	Verbal memory	HC: 0
Takahashi 2008,	23 HC	[¹¹ C]FLB 457	Hippocampus	Visual memory	HC: +
			PFC	Executive function	HC: +
Takahashi, 2007	25 HC	[¹¹ C]FLB 457	Hippocampus	Memory	HC: +
			Hippocampus	Executive function	HC: +
Lumme, 2007	32 HC	[¹¹ C]FLB 457	Right ACC	Executive function	HC: -

+ = positive linear correlation, - = negative linear correlation, 0 = no significant correlation, ∪ = U-shaped quadratic correlation, ∩ = inverted U-shaped quadratic correlation. All results reflect the relationship between better performance and higher BP_{ND} levels, if error measures were used the correlation has been reversed. HC = healthy control subjects, SCZ = schizophrenia patients, FEP = first episode psychosis patients.

Supplementary Table 2 lists all the cognitive domains of the MCCB as well as the test of Executive Function (WCST), and the raw values of these for patients and controls in the present study. P-values have not been corrected for multiple comparisons.

Supplementary Table 2. Cognitive domains and tests for exploratory analyses (raw scores, mean (standard deviation))

Cognitive domain	FEP	HC	t-value	df	p-value
Cognitive test(s)	N = 18	N = 16			
Speed of processing	67.15 (8.2)	74.77 (4.5)	-3.42	27.13	0.002*
Trail Making Test A					
BACS Symbol Coding					
Category Fluency, Animal naming					
Working memory	16.00 (3.0)	16.47 (2.2)	-0.52	30.99	0.606
WMS-III Spatial Span					
WAIS-III Letter number sequencing					
Verbal memory	26.83 (4.7)	28.94 (3.4)	-1.50	30.62	0.143
Hopkins Verbal Learning Test - Revised					
Visual memory	24.11 (6.8)	30.06 (2.7)	-3.40	22.77	0.003*
Brief Visuospatial Memory Test-Revised					
Attention	2.39 (0.6)	2.82 (0.5)	-2.13	31.66	0.041*
Continuous Performance Test – Identical Pairs Version					
Neurocognitive composite	155.38 (19.6)	174.77 (10.6)	-3.64	26.76	0.001*
All tests above + NAB Mazes					
Executive function	21.94 (11.1)	19.63 (14.4)	0.51	28.15	0.616
Wisconsin Card Sorting Test (% Errors)	N=16				

Post-hoc analyses.

Main analysis repeated without FEP who had a diagnosis of delusional disorder (N = 3).
FEP N = 15, HC N = 16

Supplementary Table 3. Subgroup analysis, main effect of cognition

	β (95% CI)	Partial r	Df	p -value
Verbal learning and D2R in DLPFC	0.096 (-0.008 – 0.200)	0.343	27	0.068
Verbal learning and D2R in Hippocampus	0.047 (-0.064 – 0.157)	0.164	27	0.395
Working memory and D2R in DLPFC	-0.058 (-0.149 – 0.033)	-0.244	27	0.203
Speed of processing and D2R in DLPFC	-0.018 (-0.158 – 0.123)	-0.050	27	0.800

Supplementary Table 4. Subgroup analyses, with added interaction effect

	β (95% CI) interaction effect	Df	p -value	Partial r FEP	Df	p -value FEP	Partial r HC	Df	p -value HC
Verbal learning D2R DLPFC	-0.118 (-0.337 – 0.100)	26	0.277	0.249	12	0.391	0.443	13	0.098
Verbal learning D2R Hippocampus	-0.124 (-0.356 – 0.108)	26	0.283	0.018	12	0.951	0.419	13	0.120
Working memory D2R DLPFC	0.114 (-0.070 – 0.299)	26	0.214	-0.054	12	0.854	-0.402	13	0.138
Speed of processing D2R DLPFC	0.086 (-0.227 – 0.400)	26	0.576	-0.003	12	0.990	-0.114	13	0.685

Main analysis repeated with gender as a covariate.

Supplementary Table 5.

	Original results (age + patient/HC status)		Results with gender as added covariate	
	β (95% CI)	p -value	β (95% CI)	p -value
Verbal learning and D2R in DLPFC	0.074 (-0.023 – 0.171)	0.131	0.076 (-0.024 – 0.175)	0.130
Verbal learning and D2R in Hippocampus	0.031 (-0.069 – 0.132)	0.529	0.034 (-0.068 – 0.136)	0.506
Working memory and D2R in DLPFC	-0.039 (-0.123 – 0.044)	0.341	-0.039 (-0.125 – 0.047)	0.365
Speed of processing and D2R in DLPFC	-0.013 (-0.140 – 0.115)	0.841	-0.014 (-0.144 – 0.116)	0.826

The following tables (Supplementary Tables 6-10) present all the exploratory analyses conducted.

Supplementary Table 6. Exploratory analyses of D2-R levels and main effect of cognition

Region of interest															
	DLPFC			Hippocampus			Thalamus			ACC			Temporal cortex		
Cognitive domain	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value
Verbal learning	-	-	-	-	-	-	-0.072 (-0.333 – 0.189)	-0.102	0.578	0.029 (-0.073 – 0.131)	0.107	0.560	0.120 (-0.024 – 0.263)	0.297	0.098
Working memory	-	-	-	0.031 (-0.053 – 0.115)	0.136	0.459	0.038 (-0.182 – 0.258)	0.065	0.725	0.005 (-0.081 – 0.091)	0.023	0.903	-0.019 (-0.145 – 0.107)	-0.057	0.756
Speed of processing	-	-	-	0.040 (-0.087 – 0.167)	0.116	0.527	0.053 (-0.278 – 0.384)	0.060	0.745	0.030 (-0.099 – 0.159)	0.087	0.637	0.000 (-0.190 – 0.190)	0.000	0.999
Attention	0.068 (-0.029 – 0.164)	0.253	0.162	0.140 (0.054 – 0.225)	0.521	0.002	0.208 (-0.039 – 0.456)	0.300	0.095	0.089 (-0.007 – 0.184)	0.326	0.068	0.188 (0.058 – 0.319)	0.474	0.006
Visual learning	0.029 (-0.081 – 0.139)	0.097	0.599	-0.005 (-0.115 – 0.106)	-0.015	0.935	-0.020 (-0.306 – 0.267)	-0.026	0.889	0.051 (-0.059 – 0.161)	0.170	0.353	-0.004 (-0.168 – 0.160)	-0.009	0.963
Executive function N = 32	0.060 (-0.039 – 0.159)	0.229	0.224	-0.005 (-0.106 – 0.095)	-0.021	0.913	0.121 (-0.141 – 0.383)	0.176	0.352	0.056 (-0.046 – 0.158)	0.208	0.269	0.096 (-0.051 – 0.243)	0.246	0.191
General cognitive ability	0.013 (-0.112 – 0.138)	0.039	0.830	0.037 (-0.087 – 0.161)	0.110	0.551	0.000 (-0.324 – 0.324)	0.000	0.998	0.043 (-0.082 – 0.169)	0.128	0.486	0.028 (-0.157 – 0.213)	0.057	0.759

Supplementary Table 7. Exploratory regression analyses of D2-R levels and cognition with interaction effect

Region of interest										
	DLPFC		Hippocampus		Thalamus		ACC		Temporal cortex	
	Interaction		Interaction		Interaction		Interaction		Interaction	
Cognitive domain	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Verbal learning	-	-	-	-	-0.419 (-0.978 – 0.139)	0.136	-0.153 (-0.372 – 0.066)	0.164	-0.124 (-0.438 – 0.191)	0.428
Working memory	-	-	0.028 (-0.154 – 0.209)	0.759	0.120 (-0.354 – 0.594)	0.609	0.119 (-0.061 – 0.300)	0.187	0.097 (-0.173 – 0.367)	0.468
Speed of processing	-	-	-0.109 (-0.409 – 0.190)	0.461	0.102 (-0.687 – 0.890)	0.794	0.051 (-0.256 – 0.359)	0.735	0.038 (-0.414 – 0.489)	0.866
Attention	-0.064 (-0.267 – 0.140)	0.526	0.006 (-0.175 – 0.187)	0.947	-0.254 (-0.770 – 0.262)	0.323	-0.020 (-0.223 – 0.183)	0.843	-0.006 (-0.283 – 0.271)	0.966
Visual learning	-0.160 (-0.506 – 0.188)	0.355	-0.380 (-0.704 - 0.057)	0.023	-0.397 (-1.303 – 0.510)	0.378	-0.043 (-0.397 – 0.311)	0.805	-0.387 (-0.891 – 0.117)	0.128
Executive function N = 32	-0.021 (-0.230 – 0.188)	0.839	-0.026 (-0.238 – 0.187)	0.805	0.346 (-0.190 – 0.881)	0.197	-0.021 (-0.236 – 0.194)	0.844	-0.060 (-0.370 – 0.250)	0.693
General cognitive ability	0.008 (-0.314 – 0.330)	0.961	-0.247 (-0.553 – 0.059)	0.110	-0.295 (-1.124 – 0.534)	0.472	0.007 (-0.317 – 0.331)	0.965	-0.096 (-0.572 – 0.380)	0.683

Supplementary Table 8. Exploratory analyses of interaction effect continued, partial r values for FEP and HC separately

Region of interest																				
	DLPFC				Hippocampus				Thalamus				ACC				Temporal cortex			
	FEP		HC		FEP		HC		FEP		HC		FEP		HC		FEP		HC	
Cognitive domain	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value	Partial <i>r</i>	p-value
Verbal learning	-	-	-	-	-	-	-	-	-0.293	0.254	0.288	0.297	-0.062	0.814	0.424	0.116	0.229	0.377	0.442	0.099
Working memory	-	-	-	-	0.177	0.497	0.049	0.864	0.135	0.607	-0.066	0.816	0.205	0.430	-0.291	0.292	0.038	0.886	-0.229	0.412
Speed of processing	-	-	-	-	0.053	0.841	0.270	0.330	0.095	0.717	-0.031	0.912	0.149	0.568	-0.055	0.847	0.026	0.922	-0.065	0.819
Attention	0.221	0.394	0.321	0.243	0.539	0.026	0.489	0.064	0.167	0.522	0.542	0.037	0.317	0.216	0.340	0.216	0.492	0.045	0.446	0.096
Visual learning	0.014	0.959	0.260	0.349	-0.184	0.479	0.613	0.015	-0.099	0.706	0.249	0.371	0.210	0.419	0.144	0.608	-0.126	0.631	0.402	0.138
Executive function	0.224	0.421	0.363	0.183	-0.066	0.815	0.005	0.987	0.371	0.174	-0.050	0.860	0.146	0.603	0.260	0.350	0.144	0.609	0.356	0.194
General cognitive ability	0.060	0.819	0.017	0.952	-0.037	0.890	0.499	0.058	-0.072	0.783	0.204	0.466	0.158	0.544	0.072	0.799	0.024	0.928	0.142	0.613

Supplementary Table 9. Exploratory analyses of baseline D2-R levels and cognitive function at 1.5 year follow-up. Only FEP, N = 12

Region of interest															
	DLPFC			Hippocampus			Thalamus			ACC			Temporal cortex		
Cognitive domain	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value
Verbal learning	-0.114 (-0.334 – 0.107)	-0.362	0.274	0.157 (-0.197 – 0.510)	0.317	0.342	0.139 (0.421 – 5.502)	0.114	0.739	0.048 (-0.266 – 0.361)	0.114	0.740	-0.167 (-0.519 – 0.185)	-0.336	0.312
Working memory	-0.049 (-0.162 – 0.064)	-0.310	0.354	0.066 (-0.114 – 0.246)	0.266	0.429	-0.104 (-0.556 – 0.350)	-0.170	0.618	-0.031 (-0.187 – 0.126)	-0.146	0.669	-0.048 (-0.232 – 0.136)	-0.192	0.572
Speed of processing	-0.018 (-0.172 – 0.136)	-0.090	0.793	0.069 (-0.169 – 0.307)	0.214	0.528	0.003 (-0.596 – 0.602)	0.004	0.991	0.006 (-0.200 – 0.213)	0.022	0.948	0.017 (-0.228 – 0.261)	0.051	0.882
Attention	-0.003 (-0.144 – 0.137)	-0.018	0.959	0.179 (0.003 – 0.354)	0.608	0.047	0.163 (-0.367 – 0.694)	0.226	0.504	0.034 (-0.152 – 0.220)	0.137	0.689	0.071 (-0.145 – 0.286)	0.240	0.477
Visual learning	0.037 (-0.115 – 0.188)	0.180	0.597	0.080 (-0.115 – 0.315)	0.248	0.463	0.178 (-0.403 – 0.760)	0.225	0.505	0.029 (-0.176 – 0.233)	0.105	0.760	0.050 (-0.190 – 0.290)	0.155	0.650
General cognitive ability	-0.036 (-0.191 – 0.119)	-0.172	0.613	0.097 (-0.140 – 0.335)	0.295	0.378	0.024 (-0.587 – 0.634)	0.029	0.933	0.002 (-0.209 – 0.213)	0.007	0.984	-0.017 (-0.265 – 0.232)	-0.050	0.884

Supplementary Table 10. Exploratory analyses of baseline D2-R levels and change in cognitive function from baseline to 1.5 year follow-up. Only FEP, N = 12

Region of interest															
	DLPFC			Hippocampus			Thalamus			ACC			Temporal cortex		
Cognitive domain	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value	β (95% CI)	Partial <i>r</i>	p-value
Verbal learning	-0.021 (-0.161 – 0.120)	-0.333	0.747	0.100 (-0.117 – 0.311)	0.323	0.333	0.269 (-0.246 – 0.784)	0.366	0.268	0.096 (-0.081 – 0.272)	0.379	0.251	-0.064 (-0.282 – 0.154)	-0.216	0.523
Working memory	-0.034 (-0.198 – 0.131)	-0.154	0.652	0.028 (-0.238 – 0.293)	0.078	0.820	-0.463 (-1.012 – 0.086)	-0.536	0.089	-0.162 (-0.350 – 0.026)	-0.544	0.084	-0.026 (-0.288 – 0.237)	-0.073	0.830
Speed of processing	0.019 (-0.309 – 0.348)	0.044	0.897	0.172 (-0.338 – 0.681)	0.246	0.466	-0.017 (-1.302 – 1.269)	-0.010	0.977	0.022 (-0.420 – 0.465)	0.038	0.912	0.055 (-0.463 – 0.573)	0.080	0.817
Attention	0.132 (-0.126 – 0.389)	0.036	0.277	0.303 (-0.074 – 0.679)	0.518	0.103	0.763 (-0.149 – 1.675)	0.534	0.091	0.214 (-0.121 – 0.549)	0.434	0.182	0.188 (-0.225 – 0.600)	0.324	0.330
Visual learning	0.038 (-0.069 – 0.144)	0.258	0.444	0.073 (-0.094 – 0.239)	0.312	0.351	0.034 (-0.394 – 0.463)	0.060	0.860	-0.020 (-0.167 – 0.127)	-0.103	0.764	0.060 (-0.107 – 0.228)	0.262	0.436
General cognitive ability	0.029 (-0.249 – 0.306)	0.077	0.821	0.323 (-0.049 – 0.694)	0.548	0.081	0.075 (-1.011 – 1.160)	0.052	0.879	-0.036 (-0.410 – 0.338)	-0.072	0.832	0.063 (-0.374 – 0.499)	0.107	0.754

Supplementary Methods:

The WCST was not used in any of the longitudinal analyses, due to significant learning effects.

Supplementary Table 11. Demographic and clinical data of [¹¹C]FLB 457 patients who completed cognitive testing at follow-up

	FEP N=12
Gender (male/female)	8/4
Age	30.3 (7.7)
Education in years	14.9 (4.4) N = 10
Diagnosis	
Schizophrenia	4
Psychotic disorder NOS	3
No diagnosis	1
Delusional disorder	2
Schizoaffective disorder	1
Depressive episode	1
PANSS	
Positive	11.8 (4.1)
Negative	10.2 (3.2)
General	27.6 (8.9)
Total	49.6 (13.1)
Level of functioning	
CGI	2.5 (1.5)
GAF	62.1 (20.3)
Medication at time of testing	
Anti-psychotics	4 N = 10
Anti-depressants	0 N = 9
Mood stabilizers	0 N = 10
Benzodiazepines	2 N = 6

Detailed information on age correction of test scores:

Cognitive test scores were age-corrected using linear regression (Raw Cognitive Test Score ~ Age) using the full study sample (see Supplementary Table 2 for demographics). The resulting residuals were used as the cognitive variables in all analyses. The match between raw scores and age-corrected residuals were plotted and inspected visually. Cognitive composite measures, (Speed of Processing (SoP), Working Memory (WM) and Neurocognitive composite (NC)) were constructed as described in the MCCB manual (Nuechterlein & Green, 2006) by adding together the relevant tests and dividing this by the number of tests. One of the test scores included in the SoP domain (TMT) was flipped, so that higher values represented better performance. Before analysis, all cognitive measures were standardized into z-values, with a mean of 0 and a standard deviation of 1.

Supplementary Table 12, demographic data on larger cohort at baseline, used to construct age corrected variables.

	FEP N=83	HC N=59
Gender (male/female)	50/33	28/31
Age	28.9 (7.9)	27.1 (5.6)
Education in years	14.0 (3.1) N=72	14.9 (2.2) N = 58
Duration of illness (months)	11.4 (17.2) N = 69	-
Diagnosis		-
Schizophrenia	18	
Schizophreniform disorder	26	
Psychotic disorder NOS	28	
Delusional disorder	5	
Schizoaffective disorder	2	
Brief psychotic disorder	3	
Severe depressive disorder with psychotic features	1	
PANSS		-
Positive	18.2 (5.8)	
Negative	16.6 (6.7)	
General	36.5 (10.7)	
Total	71.3 (19.6)	
Level of functioning		-
CGI	4.4 (1.2)	
GAF	42.2 (13.1) N = 82	
Medication at time of testing		-
Anti-psychotics	43	
Anti-depressants	8	
Mood stabilizers	2	
Benzodiazepines	43	

Supplementary Table 13, demographic data on larger cohort at 1,5 year follow-up, used to construct age corrected variables.

	FEP N=37	HC N=25
Gender (male/female)	21/16	11/14
Age	32.4 (9.2)	28.2 (6.3)
Education in years	14.1 (3.2) N = 35	16.2 (2.6)
Diagnosis		-
Schizophrenia	21	
Psychotic disorder NOS	5	
No diagnosis	3	
Delusional disorder	2	
Schizoaffective disorder	2	
Depressive episode	2	
Brief psychotic disorder	1	
Residual Schizophrenia	1	
PANSS		-
Positive	11.4 (3.7)	
Negative	13.8 (5.8)	
General	27.4 (7.5)	
Total	52.6 (13.8)	
Level of functioning		-
CGI	2.7 (1.4) N = 36	
GAF	64.2 (18.1) N = 36	
Medication at time of testing		-
Anti-psychotics	15 N = 31	
Anti-depressants	7 N = 30	
Mood stabilizers	2 N = 35	
Benzodiazepines	3 N = 24	