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APPENDIX A: STATISTICS OUTPUTS

Appendix A1 Tests of within-subjects effects in perinatal groups for the spatial discrimination component of the double Y-maze

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
day	Sphericity Assumed	10400.144	24	433.339	32.177	.000
	Greenhouse-Geisser	10400.144	1.082	9609.978	32.177	.000
	Huynh-Feldt	10400.144	1.232	8441.689	32.177	.000
	Lower-bound	10400.144	1.000	10400.144	32.177	.000
day * Group	Sphericity Assumed	731.403	24	30.475	2.263	.001
	Greenhouse-Geisser	731.403	1.082	675.834	2.263	.161
	Huynh-Feldt	731.403	1.232	593.672	2.263	.156
	Lower-bound	731.403	1.000	731.403	2.263	.163
Error(day)	Sphericity Assumed	3232.152	240	13.467		
	Greenhouse-Geisser	3232.152	10.822	298.658		
	Huynh-Feldt	3232.152	12.320	262.350		
	Lower-bound	3232.152	10.000	323.215		

Appendix A2 Tests of between-subjects effects in perinatal groups for the spatial discrimination component of the double-Y maze

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	2832066.972	1	2832066.972	153092.582	.000
Group	39.417	1	39.417	2.131	.175
Error	184.990	10	18.499		

Appendix A3 Tests of within-subjects effects in perinatal groups for the delayed alternation component of the double Y-maze

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
day	Sphericity Assumed	35772.282	24	1490.512	16.028	.000
	Greenhouse-Geisser	35772.282	6.696	5342.305	16.028	.000
	Huynh-Feldt	35772.282	23.715	1508.443	16.028	.000
	Lower-bound	35772.282	1.000	35772.282	16.028	.003
day * Group	Sphericity Assumed	15131.901	24	630.496	6.780	.000
	Greenhouse-Geisser	15131.901	6.696	2259.828	6.780	.000
	Huynh-Feldt	15131.901	23.715	638.081	6.780	.000
	Lower-bound	15131.901	1.000	15131.901	6.780	.026
Error(day)	Sphericity Assumed	22318.344	240	92.993		
	Greenhouse-Geisser	22318.344	66.960	333.307		
	Huynh-Feldt	22318.344	237.147	94.112		
	Lower-bound	22318.344	10.000	2231.834		

Appendix A4 Tests of between-subjects effects in perinatal groups for the delayed alternation component of the double-Y maze

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	1169448.145	1	1169448.145	3135.931	.000
Group	3608.108	1	3608.108	9.675	.011
Error	3729.189	10	372.919		

Appendix A5 Tests of within-subjects effects in perinatal groups for T1 of the object recognition task

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	4079.034	2	2039.517	1.402	.257
	Greenhouse-Geisser	4079.034	1.798	2268.842	1.402	.257
	Huynh-Feldt	4079.034	2.000	2039.517	1.402	.257
	Lower-bound	4079.034	1.000	4079.034	1.402	.249
delay * Group	Sphericity Assumed	344.279	2	172.139	.118	.889
	Greenhouse-Geisser	344.279	1.798	191.495	.118	.869
	Huynh-Feldt	344.279	2.000	172.139	.118	.889
	Lower-bound	344.279	1.000	344.279	.118	.734
Error(delay)	Sphericity Assumed	64010.068	44	1454.774		
	Greenhouse-Geisser	64010.068	39.553	1618.350		
	Huynh-Feldt	64010.068	44.000	1454.774		
	Lower-bound	64010.068	22.000	2909.549		

Appendix A6 Tests of between-subjects effects in perinatal groups for T1 of the object recognition task

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	452184.650	1	452184.650	255.866	.000
Group	734.083	1	734.083	.415	.526
Error	38879.936	22	1767.270		

Appendix A7 Tests of within-subjects effects in adolescent groups for T1 of the object recognition task

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	7720.005	2	3860.003	5.220	.009
	Greenhouse-Geisser	7720.005	1.541	5008.132	5.220	.016
	Huynh-Feldt	7720.005	1.711	4513.099	5.220	.013
	Lower-bound	7720.005	1.000	7720.005	5.220	.032
delay * Group	Sphericity Assumed	1667.847	2	833.923	1.128	.333
	Greenhouse-Geisser	1667.847	1.541	1081.968	1.128	.322
	Huynh-Feldt	1667.847	1.711	975.020	1.128	.327
	Lower-bound	1667.847	1.000	1667.847	1.128	.300
Error(delay)	Sphericity Assumed	32536.188	44	739.459		
	Greenhouse-Geisser	32536.188	33.913	959.405		
	Huynh-Feldt	32536.188	37.633	864.572		
	Lower-bound	32536.188	22.000	1478.918		

Appendix A8 Tests of between-subjects effects in adolescent groups for T1 of the object recognition task

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	444687.369	1	444687.369	185.678	.000
Group	1124.961	1	1124.961	.470	.500
Error	52688.711	22	2394.941		

Appendix A9 Tests of within-subjects effects in adult groups for T1 of the object recognition task

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	520.330	2	260.165	.382	.684
	Greenhouse-Geisser	520.330	1.796	289.767	.382	.662
	Huynh-Feldt	520.330	2.000	260.165	.382	.684
	Lower-bound	520.330	1.000	520.330	.382	.543
delay * Group	Sphericity Assumed	882.003	2	441.002	.648	.528
	Greenhouse-Geisser	882.003	1.796	491.179	.648	.512
	Huynh-Feldt	882.003	2.000	441.002	.648	.528
	Lower-bound	882.003	1.000	882.003	.648	.429
Error(delay)	Sphericity Assumed	29929.680	44	680.220		
	Greenhouse-Geisser	29929.680	39.505	757.615		
	Huynh-Feldt	29929.680	44.000	680.220		
	Lower-bound	29929.680	22.000	1360.440		

Appendix A10 Tests of between-subjects effects in adult groups for T1 of the object recognition task

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	182952.005	1	182952.005	159.825	.000
Group	36.980	1	36.980	.032	.859
Error	25183.462	22	1144.703		

Appendix A11 Tests of within-subjects effects in perinatal groups for T2 of the object recognition task

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	537.224	2	268.612	1.594	.215
	Greenhouse-Geisser	537.224	1.840	291.906	1.594	.217
	Huynh-Feldt	537.224	2.000	268.612	1.594	.215
	Lower-bound	537.224	1.000	537.224	1.594	.220
delay * Group	Sphericity Assumed	94.376	2	47.188	.280	.757
	Greenhouse-Geisser	94.376	1.840	51.280	.280	.739
	Huynh-Feldt	94.376	2.000	47.188	.280	.757
	Lower-bound	94.376	1.000	94.376	.280	.602
Error(delay)	Sphericity Assumed	7413.526	44	168.489		
	Greenhouse-Geisser	7413.526	40.489	183.100		
	Huynh-Feldt	7413.526	44.000	168.489		
	Lower-bound	7413.526	22.000	336.978		

Appendix A12 Tests of between-subjects effects in perinatal groups for T2 of the object recognition task

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	251535.599	1	251535.599	1259.423	.000
Group	899.766	1	899.766	4.505	.045
Error	4393.904	22	199.723		

Appendix A13 Tests of within-subjects effects in adolescent groups for T2 of the object recognition task

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	3.378	2	1.689	.008	.992
	Greenhouse-Geisser	3.378	1.983	1.703	.008	.992
	Huynh-Feldt	3.378	2.000	1.689	.008	.992
	Lower-bound	3.378	1.000	3.378	.008	.930
delay * Group	Sphericity Assumed	96.136	2	48.068	.224	.800
	Greenhouse-Geisser	96.136	1.983	48.478	.224	.798
	Huynh-Feldt	96.136	2.000	48.068	.224	.800
	Lower-bound	96.136	1.000	96.136	.224	.641
Error(delay)	Sphericity Assumed	9440.729	44	214.562		
	Greenhouse-Geisser	9440.729	43.627	216.395		
	Huynh-Feldt	9440.729	44.000	214.562		
	Lower-bound	9440.729	22.000	429.124		

Appendix A14 Tests of between-subjects effects in adolescent groups for T2 of the object recognition task

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	268606.547	1	268606.547	1172.789	.000
Group	2127.936	1	2127.936	9.291	.006
Error	5038.708	22	229.032		

Appendix A15 Tests of within-subjects effects in adult groups for T2 of the object recognition task

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	626.549	2	313.275	1.277	.289
	Greenhouse-Geisser	626.549	1.871	334.806	1.277	.288
	Huynh-Feldt	626.549	2.000	313.275	1.277	.289
	Lower-bound	626.549	1.000	626.549	1.277	.271
delay * Group	Sphericity Assumed	209.005	2	104.502	.426	.656
	Greenhouse-Geisser	209.005	1.871	111.685	.426	.643
	Huynh-Feldt	209.005	2.000	104.502	.426	.656
	Lower-bound	209.005	1.000	209.005	.426	.521
Error(delay)	Sphericity Assumed	10793.371	44	245.304		
	Greenhouse-Geisser	10793.371	41.170	262.164		
	Huynh-Feldt	10793.371	44.000	245.304		
	Lower-bound	10793.371	22.000	490.608		

Appendix A16 Tests of between-subjects effects in adult groups for T2 of the object recognition task

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	261727.729	1	261727.729	1397.128	.000
Group	874.051	1	874.051	4.666	.042
Error	4121.318	22	187.333		

Appendix A17 Tests of within-subjects effects in perinatal groups for T1 locomotor activity

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	3194.622	2	1597.311	1.016	.371
	Greenhouse-Geisser	3194.622	1.692	1887.914	1.016	.361
	Huynh-Feldt	3194.622	1.901	1680.225	1.016	.368
	Lower-bound	3194.622	1.000	3194.622	1.016	.325
delay * Group	Sphericity Assumed	302.255	2	151.127	.096	.909
	Greenhouse-Geisser	302.255	1.692	178.622	.096	.879
	Huynh-Feldt	302.255	1.901	158.972	.096	.900
	Lower-bound	302.255	1.000	302.255	.096	.759
Error(delay)	Sphericity Assumed	69205.287	44	1572.847		
	Greenhouse-Geisser	69205.287	37.227	1859.000		
	Huynh-Feldt	69205.287	41.829	1654.491		
	Lower-bound	69205.287	22.000	3145.695		

Appendix A18 Tests of between-subjects effects in perinatal groups for T1 locomotor activity

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	7633423.383	1	7633423.383	8911.873	.000
Group	2180.549	1	2180.549	2.546	.125
Error	18843.998	22	856.545		

Appendix A19 Tests of within-subjects effects in adolescent groups for T1 locomotor activity

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	6547.105	2	3273.553	1.512	.232
	Greenhouse-Geisser	6547.105	1.806	3624.911	1.512	.233
	Huynh-Feldt	6547.105	2.000	3273.553	1.512	.232
	Lower-bound	6547.105	1.000	6547.105	1.512	.232
delay * Group	Sphericity Assumed	1835.445	2	917.722	.424	.657
	Greenhouse-Geisser	1835.445	1.806	1016.224	.424	.637
	Huynh-Feldt	1835.445	2.000	917.722	.424	.657
	Lower-bound	1835.445	1.000	1835.445	.424	.522
Error(delay)	Sphericity Assumed	95241.833	44	2164.587		
	Greenhouse-Geisser	95241.833	39.735	2396.918		
	Huynh-Feldt	95241.833	44.000	2164.587		
	Lower-bound	95241.833	22.000	4329.174		

Appendix A20 Tests of between-subjects effects in adolescent groups for T1 locomotor activity

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	7966895.052	1	7966895.052	5407.436	.000
Group	3031.862	1	3031.862	2.058	.165
Error	32413.088	22	1473.322		

Appendix A21 Tests of within-subjects effects in adult groups for T1 locomotor activity

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	3231.077	2	1615.539	1.408	.255
	Greenhouse-Geisser	3231.077	1.626	1987.181	1.408	.256
	Huynh-Feldt	3231.077	1.817	1778.084	1.408	.256
	Lower-bound	3231.077	1.000	3231.077	1.408	.248
delay * Group	Sphericity Assumed	1462.084	2	731.042	.637	.534
	Greenhouse-Geisser	1462.084	1.626	899.213	.637	.503
	Huynh-Feldt	1462.084	1.817	804.595	.637	.520
	Lower-bound	1462.084	1.000	1462.084	.637	.433
Error(delay)	Sphericity Assumed	50491.804	44	1147.541		
	Greenhouse-Geisser	50491.804	35.771	1411.524		
	Huynh-Feldt	50491.804	39.978	1262.999		
	Lower-bound	50491.804	22.000	2295.082		

Appendix A22 Tests of between-subjects effects in adult groups for T1 locomotor activity

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	6192693.662	1	6192693.662	1643.635	.000
Group	59.881	1	59.881	.016	.901
Error	82889.023	22	3767.683		

Appendix A23 Tests of within-subjects effects in perinatal groups for T2 locomotor activity

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	4413.816	2	2206.908	1.706	.193
	Greenhouse-Geisser	4413.816	1.827	2415.915	1.706	.196
	Huynh-Feldt	4413.816	2.000	2206.908	1.706	.193
	Lower-bound	4413.816	1.000	4413.816	1.706	.205
delay * Group	Sphericity Assumed	442.204	2	221.102	.171	.843
	Greenhouse-Geisser	442.204	1.827	242.042	.171	.825
	Huynh-Feldt	442.204	2.000	221.102	.171	.843
	Lower-bound	442.204	1.000	442.204	.171	.683
Error(delay)	Sphericity Assumed	56916.500	44	1293.557		
	Greenhouse-Geisser	56916.500	40.193	1416.064		
	Huynh-Feldt	56916.500	44.000	1293.557		
	Lower-bound	56916.500	22.000	2587.114		

Appendix A24 Tests of between-subjects effects in perinatal groups for T2 locomotor activity

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	7450794.047	1	7450794.047	6143.546	.000
Group	299.300	1	299.300	.247	.624
Error	26681.248	22	1212.784		

Appendix A25 Tests of within-subjects effects in adolescent groups for T2 locomotor activity

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	5483.944	2	2741.972	2.312	.111
	Greenhouse-Geisser	5483.944	1.906	2876.850	2.312	.114
	Huynh-Feldt	5483.944	2.000	2741.972	2.312	.111
	Lower-bound	5483.944	1.000	5483.944	2.312	.143
delay * Group	Sphericity Assumed	282.356	2	141.178	.119	.888
	Greenhouse-Geisser	282.356	1.906	148.122	.119	.879
	Huynh-Feldt	282.356	2.000	141.178	.119	.888
	Lower-bound	282.356	1.000	282.356	.119	.733
Error(delay)	Sphericity Assumed	52192.603	44	1186.196		
	Greenhouse-Geisser	52192.603	41.937	1244.545		
	Huynh-Feldt	52192.603	44.000	1186.196		
	Lower-bound	52192.603	22.000	2372.391		

Appendix A26 Tests of between-subjects effects in adolescent groups for T2 locomotor activity

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	7420849.295	1	7420849.295	4013.906	.000
Group	5396.052	1	5396.052	2.919	.102
Error	40673.268	22	1848.785		

Appendix A27 Tests of within-subjects effects in adult groups for T2 locomotor activity

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
delay	Sphericity Assumed	23245.165	2	11622.583	10.412	.000
	Greenhouse-Geisser	23245.165	1.759	13218.218	10.412	.000
	Huynh-Feldt	23245.165	1.986	11702.707	10.412	.000
	Lower-bound	23245.165	1.000	23245.165	10.412	.004
delay * Group	Sphericity Assumed	3043.256	2	1521.628	1.363	.266
	Greenhouse-Geisser	3043.256	1.759	1730.528	1.363	.266
	Huynh-Feldt	3043.256	1.986	1532.118	1.363	.266
	Lower-bound	3043.256	1.000	3043.256	1.363	.255
Error(delay)	Sphericity Assumed	49115.929	44	1116.271		
	Greenhouse-Geisser	49115.929	38.689	1269.521		
	Huynh-Feldt	49115.929	43.699	1123.966		
	Lower-bound	49115.929	22.000	2232.542		

Appendix A28 Tests of between-subjects effects in adult groups for T2 locomotor activity

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	5588301.272	1	5588301.272	1199.378	.000
Group	1343.884	1	1343.884	.288	.597
Error	102505.282	22	4659.331		

Appendix A29 Independent samples *t*-test in perinatal groups for total non-aggressive social interaction behaviours (sniffing, following, grooming, mounting, and crawling under/over the conspecific)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
Source		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Total	Equal variances assumed	.032	.860	3.342	22	.003	37.0000	11.0696	14.0431	59.9569
	Equal variances not assumed			3.342	22.000	.003	37.0000	11.0696	14.0430	59.9570

Appendix A30 Independent samples *t*-test in adolescent groups for total non-aggressive social interaction behaviours (sniffing, following, grooming, mounting, and crawling under/over the conspecific)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
Source		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Total	Equal variances assumed	10.502	.004	3.294	22	.003	30.7083	9.3218	11.3762	50.0405
	Equal variances not assumed			3.294	14.648	.005	30.7083	9.3218	10.7978	50.6188

Appendix A31 Independent samples *t*-test in adult groups for total non-aggressive social interaction behaviours (sniffing, following, grooming, mounting, and crawling under/over the conspecific)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
Source		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Total	Equal variances assumed	9.253	.006	3.612	22	.002	51.2167	14.1802	21.8087	80.6247
	Equal variances not assumed			3.612	15.845	.002	51.2167	14.1802	21.1320	81.3013

Appendix A32 Independent samples *t*-tests in perinatal groups for non-aggressive (Chapter 5) and aggressive (Chapter 6) social behaviours

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
Source		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Sniffing	Equal variances assumed	.277	.604	2.447	22	.023	26.3500	10.7671	4.0203	48.6797
	Equal variances not assumed			2.447	21.961	.023	26.3500	10.7671	4.0180	48.6820
Following	Equal variances assumed	7.436	.012	2.718	22	.013	4.4500	1.6372	1.0546	7.8454
	Equal variances not assumed			2.718	12.119	.019	4.4500	1.6372	.8867	8.0133
Grooming	Equal variances assumed	4.840	.039	1.000	22	.328	.042	.042	-.045	.128
	Equal variances not assumed			1.000	11.000	.339	.042	.042	-.050	.133
Mounting	Equal variances assumed	.112	.741	.035	22	.972	.025	.710	-1.448	1.498
	Equal variances not assumed			.035	17.259	.972	.025	.710	-1.472	1.522
Jumping on	Equal variances assumed	.202	.657	1.300	22	.207	2.0833	1.6031	-1.2414	5.4081
	Equal variances not assumed			1.300	21.489	.208	2.0833	1.6031	-1.2460	5.4127
Wrestling/boxing	Equal variances assumed	.222	.642	1.660	22	.111	18.3000	11.0264	-4.5673	41.1673
	Equal variances not assumed			1.660	21.827	.111	18.3000	11.0264	-4.5778	41.1778
Crawling under/over	Equal variances assumed	10.075	.004	2.656	22	.014	6.133	2.310	1.344	10.923
	Equal variances not assumed			2.656	13.816	.019	6.133	2.310	1.174	11.093

Appendix A33 Independent samples *t*-tests in adolescent groups for non-aggressive (Chapter 5) and aggressive (Chapter 6) social behaviours

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
Source		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Sniffing	Equal variances assumed	9.271	.006	3.518	22	.002	24.6083	6.9952	10.1011	39.1156
	Equal variances not assumed			3.518	15.599	.003	24.6083	6.9952	9.7481	39.4686
Following	Equal variances assumed	18.169	.000	2.318	22	.030	3.6417	1.5712	.3831	6.9002
	Equal variances not assumed			2.318	12.016	.039	3.6417	1.5712	.2187	7.0646
Grooming	Equal variances assumed	1.720	.203	.553	22	.586	.3417	.6183	-.9406	1.6239
	Equal variances not assumed			.553	13.006	.590	.3417	.6183	-.9940	1.6773
Kicking	Equal variances assumed	2.283	.145	.687	22	.499	.042	.061	-.084	.167
	Equal variances not assumed			.687	12.784	.504	.042	.061	-.090	.173
Mounting	Equal variances assumed	2.932	.101	-.024	22	.981	-.008	.344	-.721	.705
	Equal variances not assumed			-.024	16.085	.981	-.008	.344	-.737	.720
Jumping on	Equal variances assumed	13.494	.001	2.680	22	.014	2.433	.908	.550	4.316
	Equal variances not assumed			2.680	13.215	.019	2.433	.908	.475	4.392
Wrestling/boxing	Equal variances assumed	7.410	.012	.017	22	.987	.142	8.536	-17.561	17.844
	Equal variances not assumed			.017	17.164	.987	.142	8.536	-17.855	18.138
Crawling under/over	Equal variances assumed	3.530	.074	1.499	22	.148	2.125	1.417	-.815	5.065
	Equal variances not assumed			1.499	18.261	.151	2.125	1.417	-.850	5.100

Appendix A34 Independent samples *t*-tests in adult groups for non-aggressive (Chapter 5) and aggressive (Chapter 6) social behaviours

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Sniffing	Equal variances assumed	5.534	.028	3.909	22	.001	38.1000	9.7457	17.8886	58.3114
	Equal variances not assumed			3.909	15.892	.001	38.1000	9.7457	17.4286	58.7714
Following	Equal variances assumed	1.596	.220	1.805	22	.085	5.8250	3.2270	-.8673	12.5173
	Equal variances not assumed			1.805	19.777	.086	5.8250	3.2270	-.9112	12.5612
Grooming	Equal variances assumed	4.840	.039	1.000	22	.328	.167	.167	-.179	.512
	Equal variances not assumed			1.000	11.000	.339	.167	.167	-.200	.533
Mounting	Equal variances assumed	.339	.567	.337	22	.740	.208	.619	-1.075	1.492
	Equal variances not assumed			.337	17.526	.740	.208	.619	-1.094	1.511
Jumping on	Equal variances assumed	16.835	.000	2.823	22	.010	2.2083	.7824	.5858	3.8309
	Equal variances not assumed			2.823	11.895	.016	2.2083	.7824	.5020	3.9147
Wrestling/boxing	Equal variances assumed	9.468	.006	1.497	22	.149	4.6667	3.1167	-1.7969	11.1303
	Equal variances not assumed			1.497	11.018	.162	4.6667	3.1167	-2.1918	11.5251
Crawling under/over	Equal variances assumed	5.648	.027	1.905	22	.070	6.9167	3.6313	-.6141	14.4474
	Equal variances not assumed			1.905	15.174	.076	6.9167	3.6313	-.8155	14.6488

Appendix A35 Independent samples *t*-test in perinatal groups for emergence latency (emergence test)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Emergence latency	Equal variances assumed	6.705	.017	-1.607	22	.122	-19.0250	11.8406	-43.5810	5.5310
	Equal variances not assumed			-1.607	18.071	.125	-19.0250	11.8406	-43.8943	5.8443

Appendix A36 Independent samples *t*-test in adolescent groups for emergence latency (emergence test)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Emergence latency	Equal variances assumed	1.343	.259	.604	22	.552	4.092	6.779	-9.968	18.151
	Equal variances not assumed			.604	16.395	.554	4.092	6.779	-10.252	18.435

Appendix A37 Independent samples *t*-test in adult groups for emergence latency (emergence test)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Emergence latency	Equal variances assumed	.000	.985	-.670	22	.510	-1.6583	2.4742	-6.7894	3.4727
	Equal variances not assumed			-.670	21.994	.510	-1.6583	2.4742	-6.7895	3.4728

Appendix A38 Independent samples *t*-tests in perinatal groups for more emergence test behaviours

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Emergence frequency	Equal variances assumed	.123	.729	-.098	22	.923	-.083	.852	-1.851	1.685
	Equal variances not assumed			-.098	21.990	.923	-.083	.852	-1.851	1.685
Open field	Equal variances assumed	.061	.807	.533	22	.599	6.1917	11.6181	-17.9028	30.2861
	Equal variances not assumed			.533	21.373	.600	6.1917	11.6181	-17.9438	30.3272
Risk assessment	Equal variances assumed	.369	.550	-1.102	22	.282	-2.9667	2.6915	-8.5484	2.6151
	Equal variances not assumed			-1.102	21.769	.282	-2.9667	2.6915	-8.5519	2.6185
Line crosses	Equal variances assumed	.053	.819	-.089	22	.930	-.833	9.401	-20.329	18.662
	Equal variances not assumed			-.089	21.332	.930	-.833	9.401	-20.365	18.698
Hide box	Equal variances assumed	.046	.832	-.784	22	.442	-8.4917	10.8372	-30.9666	13.9832
	Equal variances not assumed			-.784	21.828	.442	-8.4917	10.8372	-30.9768	13.9935

Appendix A39 Independent samples *t*-tests in adolescent groups for more emergence test behaviours

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Emergence frequency	Equal variances assumed	1.034	.320	.361	22	.721	.250	.692	-1.186	1.686
	Equal variances not assumed			.361	17.794	.722	.250	.692	-1.206	1.706
Open field	Equal variances assumed	5.341	.031	-1.496	22	.149	-15.3917	10.2904	-36.7326	5.9493
	Equal variances not assumed			-1.496	17.868	.152	-15.3917	10.2904	-37.0224	6.2391
Risk assessment	Equal variances assumed	3.079	.093	1.363	22	.187	3.767	2.763	-1.963	9.496
	Equal variances not assumed			1.363	11.955	.198	3.767	2.763	-2.255	9.789
Line crosses	Equal variances assumed	.119	.734	.659	22	.517	4.500	6.826	-9.656	18.656
	Equal variances not assumed			.659	21.405	.517	4.500	6.826	-9.679	18.679
Hide box	Equal variances assumed	.409	.529	2.225	22	.037	17.0250	7.6507	1.1584	32.8916
	Equal variances not assumed			2.225	21.900	.037	17.0250	7.6507	1.1542	32.8958

Appendix A40 Independent samples *t*-tests in adult groups for more emergence test behaviours

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Emergence frequency	Equal variances assumed	.360	.555	1.023	22	.317	.583	.570	-.599	1.766
	Equal variances not assumed			1.023	21.519	.318	.583	.570	-.601	1.767
Open field	Equal variances assumed	.144	.708	.940	22	.358	9.4750	10.0823	-11.4345	30.3845
	Equal variances not assumed			.940	19.438	.359	9.4750	10.0823	-11.5954	30.5454
Risk assessment	Equal variances assumed	3.092	.093	-.758	22	.457	-.8417	1.1107	-3.1451	1.4618
	Equal variances not assumed			-.758	17.500	.459	-.8417	1.1107	-3.1800	1.4966
Line crosses	Equal variances assumed	.517	.480	1.219	22	.236	6.333	5.197	-4.445	17.112
	Equal variances not assumed			1.219	20.905	.237	6.333	5.197	-4.478	17.144
Hide box	Equal variances assumed	2.330	.141	-1.074	22	.295	-6.2750	5.8434	-18.3934	5.8434
	Equal variances not assumed			-1.074	19.405	.296	-6.2750	5.8434	-18.4880	5.9380

Appendix A41 Independent samples *t*-test in perinatal groups for *c-fos* immunohistochemistry

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Cort insular	Equal variances assumed	.170	.687	-.168	14	.869	-.125	.743	-1.718	1.468
	Equal variances not assumed			-.168	13.880	.869	-.125	.743	-1.719	1.469
Cort piriform	Equal variances assumed	.465	.506	-.554	14	.588	-6.625	11.948	-32.250	19.000
	Equal variances not assumed			-.554	13.532	.588	-6.625	11.948	-32.334	19.084
Med CPU	Equal variances assumed	6.214	.026	-1.850	14	.086	-2.750	1.487	-5.938	.438
	Equal variances not assumed			-1.850	8.604	.099	-2.750	1.487	-6.137	.637
NA core	Equal variances assumed	9.000	.010	-1.323	14	.207	-1.000	.756	-2.621	.621
	Equal variances not assumed			-1.323	7.000	.227	-1.000	.756	-2.787	.787
NA shell	Equal variances assumed	.803	.385	-.957	14	.355	-.625	.653	-2.025	.775
	Equal variances not assumed			-.957	9.614	.362	-.625	.653	-2.088	.838
Lat Sep ven	Equal variances assumed	1.263	.280	-1.091	14	.294	-4.250	3.895	-12.604	4.104
	Equal variances not assumed			-1.091	11.732	.297	-4.250	3.895	-12.758	4.258
BNST ld	Equal variances assumed	2.178	.162	.632	14	.537	.250	.395	-.598	1.098

	Equal variances not assumed			.632	8.537	.544	.250	.395	-.652	1.152
Amy bas nuc	Equal variances assumed	1.626	.223	.727	14	.479	1.000	1.376	-1.951	3.951
	Equal variances not assumed			.727	12.962	.480	1.000	1.376	-1.973	3.973
Amy cen nuc	Equal variances assumed	1.680	.216	1.586	14	.135	3.625	2.285	-1.276	8.526
	Equal variances not assumed			1.586	10.816	.141	3.625	2.285	-1.415	8.665
Amy med nuc	Equal variances assumed	.110	.745	-.518	14	.613	-1.625	3.139	-8.358	5.108
	Equal variances not assumed			-.518	13.152	.613	-1.625	3.139	-8.399	5.149
Peri gray dor	Equal variances assumed	3.136	.098	1.723	14	.107	3.625	2.104	-.887	8.137
	Equal variances not assumed			1.723	12.301	.110	3.625	2.104	-.947	8.197
Peri gray lat	Equal variances assumed	2.422	.142	.881	14	.393	2.500	2.837	-3.585	8.585
	Equal variances not assumed			.881	13.172	.394	2.500	2.837	-3.621	8.621
Peri gray vent	Equal variances assumed	.146	.708	-.810	14	.432	-3.125	3.859	-11.401	5.151
	Equal variances not assumed			-.810	13.626	.432	-3.125	3.859	-11.423	5.173
Hipp CA1	Equal variances assumed	13.186	.003	-1.426	14	.176	-.375	.263	-.939	.189
	Equal variances not assumed			-1.426	7.000	.197	-.375	.263	-.997	.247
Hipp CA3	Equal variances assumed	.000	1.000	.000	14	1.000	.000	.378	-.811	.811
	Equal variances not assumed			.000	14.000	1.000	.000	.378	-.811	.811

Appendix A42 Independent samples *t*-test in adolescent groups for *c-fos* immunohistochemistry

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Cort insular	Equal variances assumed	1.145	.303	-.403	14	.693	-.125	.310	-.789	.539
	Equal variances not assumed			-.403	11.713	.694	-.125	.310	-.802	.552
Cort piriform	Equal variances assumed	1.362	.263	-.292	14	.775	-2.625	8.996	-21.919	16.669
	Equal variances not assumed			-.292	9.164	.777	-2.625	8.996	-22.920	17.670
Med CPU	Equal variances assumed	.692	.419	-.298	14	.770	-.125	.420	-1.026	.776
	Equal variances not assumed			-.298	13.380	.771	-.125	.420	-1.030	.780
NA core	Equal variances assumed	.337	.571	.000	14	1.000	.000	.320	-.687	.687
	Equal variances not assumed			.000	12.489	1.000	.000	.320	-.695	.695
NA shell	Equal variances assumed	1.577	.230	-.607	14	.554	-.125	.206	-.567	.317
	Equal variances not assumed			-.607	13.093	.554	-.125	.206	-.570	.320
Lat Sep ven	Equal variances assumed	1.217	.288	.701	14	.495	1.000	1.427	-2.060	4.060
	Equal variances not assumed			.701	11.741	.497	1.000	1.427	-2.116	4.116
BNST ld	Equal variances assumed	.011	.917	.208	14	.838	.250	1.201	-2.325	2.825

	Equal variances not assumed			.208	13.998	.838	.250	1.201	-2.326	2.826
Amy bas nuc	Equal variances assumed	.039	.846	.133	14	.896	.125	.939	-1.889	2.139
	Equal variances not assumed			.133	13.985	.896	.125	.939	-1.889	2.139
Amy cen nuc	Equal variances assumed	.059	.812	-.306	14	.764	-.250	.818	-2.005	1.505
	Equal variances not assumed			-.306	13.978	.764	-.250	.818	-2.005	1.505
Amy med nuc	Equal variances assumed	.029	.867	.197	14	.847	.500	2.535	-4.938	5.938
	Equal variances not assumed			.197	12.844	.847	.500	2.535	-4.984	5.984
Peri gray dor	Equal variances assumed	2.232	.157	-.136	14	.894	-.125	.920	-2.098	1.848
	Equal variances not assumed			-.136	11.070	.894	-.125	.920	-2.148	1.898
Peri gray lat	Equal variances assumed	.433	.521	.000	14	1.000	.000	.417	-.895	.895
	Equal variances not assumed			.000	10.155	1.000	.000	.417	-.928	.928
Peri gray vent	Equal variances assumed	2.012	.178	-.758	14	.461	-1.875	2.474	-7.182	3.432
	Equal variances not assumed			-.758	12.314	.463	-1.875	2.474	-7.251	3.501
Hipp CA3	Equal variances assumed	5.444	.035	-1.000	14	.334	-.125	.125	-.393	.143
	Equal variances not assumed			-1.000	7.000	.351	-.125	.125	-.421	.171

Appendix A43 Independent samples *t*-test in adult groups for *c-fos* immunohistochemistry

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Cort insular	Equal variances assumed	.441	.517	.793	14	.441	1.000	1.261	-1.704	3.704
	Equal variances not assumed			.793	13.194	.442	1.000	1.261	-1.719	3.719
Cort piriform	Equal variances assumed	3.978	.066	.384	14	.707	3.750	9.760	-17.184	24.684
	Equal variances not assumed			.384	10.488	.708	3.750	9.760	-17.861	25.361
Med CPU	Equal variances assumed	.099	.757	-.255	14	.803	-.375	1.472	-3.533	2.783
	Equal variances not assumed			-.255	12.217	.803	-.375	1.472	-3.576	2.826
NA core	Equal variances assumed	3.316	.090	-.661	14	.519	-.500	.756	-2.121	1.121
	Equal variances not assumed			-.661	11.200	.522	-.500	.756	-2.160	1.160
NA shell	Equal variances assumed	1.679	.216	.788	14	.444	1.625	2.063	-2.800	6.050
	Equal variances not assumed			.788	11.445	.447	1.625	2.063	-2.895	6.145
Lat Sep ven	Equal variances assumed	1.079	.317	-.089	14	.930	-.125	1.407	-3.143	2.893
	Equal variances not assumed			-.089	10.737	.931	-.125	1.407	-3.231	2.981
BNST ld	Equal variances assumed	7.192	.018	1.256	14	.230	.625	.498	-.443	1.693

	Equal variances not assumed			1.256	7.000	.250	.625	.498	-.552	1.802
Amy bas nuc	Equal variances assumed	1.852	.195	.927	14	.369	1.875	2.022	-2.461	6.211
	Equal variances not assumed			.927	8.472	.379	1.875	2.022	-2.742	6.492
Amy cen nuc	Equal variances assumed	.622	.443	-1.000	14	.334	-1.250	1.250	-3.931	1.431
	Equal variances not assumed			-1.000	13.898	.334	-1.250	1.250	-3.933	1.433
Amy med nuc	Equal variances assumed	.141	.713	-1.424	14	.176	-2.250	1.580	-5.638	1.138
	Equal variances not assumed			-1.424	13.929	.176	-2.250	1.580	-5.640	1.140
Peri gray dor	Equal variances assumed	7.290	.017	.993	14	.338	1.250	1.259	-1.450	3.950
	Equal variances not assumed			.993	7.468	.352	1.250	1.259	-1.689	4.189
Peri gray lat	Equal variances assumed	.000	1.000	-.333	14	.744	-.125	.375	-.929	.679
	Equal variances not assumed			-.333	13.996	.744	-.125	.375	-.929	.679
Peri gray vent	Equal variances assumed	.819	.381	.432	14	.672	.875	2.024	-3.466	5.216
	Equal variances not assumed			.432	12.119	.673	.875	2.024	-3.530	5.280
Hipp CA1	Equal variances assumed	1.145	.303	.403	14	.693	.125	.310	-.539	.789
	Equal variances not assumed			.403	11.713	.694	.125	.310	-.552	.802
Hipp CA3	Equal variances assumed	5.444	.035	-1.000	14	.334	-.125	.125	-.393	.143
	Equal variances not assumed			-1.000	7.000	.351	-.125	.125	-.421	.171

APPENDIX B: DATA

Appendix B1 Data for spatial discrimination (SD) component of the double Y-maze for 25-day training period for perinatal vehicle (group= 1) and THC (groups= 2) treated rats

Rat	Group	SD 1	SD 2	SD 3	SD 4	SD 5	SD 6	SD 7	SD 8	SD 9	SD 10	SD 11	SD 12	SD 13
31	1	26.7	86.7	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
32	1	60.0	93.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
33	1	73.3	86.7	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
34	1	60.0	93.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
35	1	53.3	86.7	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
36	1	80.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
43	1	80.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
38	2	73.3	93.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
39	2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
40	2	86.7	93.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
41	2	56.7	93.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
42	2	73.3	93.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

SD 14	SD 15	SD 16	SD 17	SD 18	SD 19	SD 20	SD 21	SD 22	SD 23	SD 24	SD 25
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

*The number of correct entries out of 30 trials (per day) in the spatial discrimination component was converted to a percentage for each rat for each of the 25 test sessions.

Appendix B2 Data for delayed alternation (DA) component of the double Y-maze for 25-day training period for perinatal vehicle (group= 1) and THC (group= 2) treated rats

Rat	Group	DA 1	DA 2	DA 3	DA 4	DA 5	DA 6	DA 7	DA 8	DA 9	DA 10	DA 11	DA 12	DA 13
31	1	50.0	43.3	63.3	46.7	30.0	56.7	63.3	43.3	63.3	63.3	33.3	60.0	46.7
32	1	50.0	26.7	63.3	46.7	33.3	46.7	43.3	40.0	50.0	56.7	43.3	53.3	70.0
33	1	50.0	40.0	70.0	70.0	30.0	40.0	56.7	60.0	60.0	46.7	63.3	70.0	83.3
34	1	33.3	50.0	66.7	56.7	60.0	43.3	53.3	50.0	63.3	33.3	60.0	53.3	46.7
35	1	40.0	66.7	60.0	56.7	43.3	46.7	50.0	50.0	60.0	53.3	73.3	76.7	73.3
36	1	33.3	66.7	46.7	46.7	60.0	50.0	36.7	60.0	46.7	26.7	53.3	56.7	40.0
43	1	40.0	36.7	63.3	56.7	36.7	50.0	43.3	50.0	56.7	53.3	66.7	50.0	66.7
38	2	43.3	50.0	56.7	56.7	60.0	53.3	43.3	73.3	63.3	50.0	50.0	50.0	56.7
39	2	56.7	50.0	63.3	46.7	53.3	56.7	53.3	73.3	66.7	56.7	40.0	43.3	60.0
40	2	36.7	56.7	36.7	83.3	50.0	76.7	50.0	50.0	56.7	80.0	40.0	66.7	73.3
41	2	23.3	43.3	60.0	66.7	53.3	66.7	53.3	50.0	56.7	50.0	33.3	66.7	46.7
42	2	40.0	70.0	56.7	53.3	66.7	50.0	70.0	60.0	66.7	50.0	53.3	66.7	63.3

DA 14	DA 15	DA 16	DA 17	DA 18	DA 19	DA 20	DA 21	DA 22	DA 23	DA 24	DA 25
70.0	80.0	83.3	70.0	83.3	73.3	83.3	80.0	90.0	80.0	83.3	86.7
56.7	66.7	80.0	93.3	96.7	83.3	80.0	93.3	83.3	80.0	86.7	83.3
76.7	76.7	80.0	96.7	80.0	90.0	100.0	86.7	86.7	73.3	90.0	76.7
53.3	73.3	76.7	90.0	73.3	100.0	83.3	83.3	96.7	86.7	90.0	90.0
80.0	96.7	80.0	90.0	86.7	93.3	83.3	100.0	100.0	80.0	80.0	80.0
53.3	66.7	63.3	80.0	73.3	73.3	76.7	83.3	90.0	86.7	93.3	86.7
56.7	83.3	93.3	86.7	90.0	90.0	83.3	80.0	86.7	93.3	83.3	96.7
50.0	60.0	60.0	50.0	63.3	40.0	40.0	53.3	56.7	53.3	60.0	70.0
86.7	76.7	46.7	66.7	43.3	56.7	53.3	40.0	50.0	70.0	80.0	80.0
66.7	66.7	72.1	63.3	66.7	60.0	73.3	66.7	83.3	86.7	90.0	90.0
60.0	83.3	60.0	53.3	53.3	63.3	50.0	56.7	60.0	80.0	73.3	70.0
56.7	56.7	70.0	56.7	80.0	66.7	53.3	60.0	63.3	80.0	76.7	80.0

*The number of correct entries out of 30 trials (per day) in the delayed alternation component was converted to a percentage for each rat for each of the 25 test sessions.

Appendix B3 Data for trial 1 (T1) in the object recognition task for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
251	1	T1	50.4	38.1	75.5
252	1	T1	53.2	92.8	46.8
253	1	T1	70.9	139.4	76.9
254	1	T1	115.4	81.9	116.1
255	1	T1	103.5	106.3	69.5
256	1	T1	130.6	123.0	36.7
257	1	T1	103.8	92.8	48.8
258	1	T1	60.3	52.9	86.4
259	1	T1	75.0	80.6	68.0
260	1	T1	44.7	67.6	158.7
261	1	T1	62.7	45.9	14.3
262	1	T1	36.6	93.6	18.3
263	2	T1	31.1	38.7	53.2
264	2	T1	27.8	83.2	40.3
265	2	T1	55.7	186.2	85.7
266	2	T1	78.7	63.8	81.6
267	2	T1	79.7	80.9	63.3
268	2	T1	193.6	94.4	45.5
269	2	T1	109.1	78.9	100.4
270	2	T1	68.0	72.3	22.1
271	2	T1	84.0	85.7	68.0
272	2	T1	52.4	136.3	208.7
273	2	T1	61.5	104.5	118.6
274	2	T1	68.8	113.2	32.0

*Individual value represents the final duration of time (sec) attending to novel objects in each 10 minute trial for each rat.

Appendix B4 Data for trial 1 (T1) in the object recognition task for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
137	1	T1	19.5	38.8	38.6
138	1	T1	110.2	86.5	43.8
139	1	T1	84.6	117.0	57.4
140	1	T1	62.1	48.7	38.6
141	1	T1	85.6	103.3	57.3
142	1	T1	68.6	102.9	82.6
143	1	T1	98.8	186.3	95.0
144	1	T1	29.6	66.5	52.4
145	1	T1	101.4	49.3	76.8
146	1	T1	84.9	38.2	53.4
147	1	T1	51.9	75.5	49.0
148	1	T1	97.0	166.8	68.0
149	2	T1	13.7	75.9	33.9
150	2	T1	60.3	68.2	61.7
151	2	T1	99.0	168.0	86.4
152	2	T1	109.4	142.3	117.6
153	2	T1	65.9	145.8	80.3
154	2	T1	73.6	104.3	50.8
155	2	T1	72.4	64.1	41.7
156	2	T1	126.2	52.3	103.8
157	2	T1	34.8	59.4	82.1
158	2	T1	115.2	83.5	148.5
159	2	T1	27.0	51.3	44.5
160	2	T1	61.2	139.5	106.9

*Individual value represents the final duration of time (sec) attending to novel objects in each 10 minute trial for each rat.

Appendix B5 Data for trial 1 (T1) in the object recognition task for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
57	1	T1	66.6	73.5	102.0
58	1	T1	76.4	29.9	41.3
59	1	T1	71.9	26.8	33.6
60	1	T1	27.4	20.9	15.4
61	1	T1	24.6	20.0	58.5
62	1	T1	31.8	109.6	59.1
63	1	T1	69.3	44.8	68.9
64	1	T1	53.1	17.2	63.0
65	1	T1	34.4	39.7	132.9
66	1	T1	13.7	20.3	56.2
67	1	T1	22.9	38.0	17.5
68	1	T1	62.5	103.5	41.7
69	2	T1	34.3	40.1	39.9
70	2	T1	66.7	18.7	46.9
71	2	T1	49.8	139.6	48.9
72	2	T1	43.3	33.6	47.0
73	2	T1	33.0	36.9	47.6
74	2	T1	96.4	135.8	67.2
75	2	T1	27.3	26.7	42.8
76	2	T1	77.4	34.9	57.0
77	2	T1	58.1	31.8	46.8
78	2	T1	37.7	30.1	70.4
79	2	T1	18.3	54.4	44.9
80	2	T1	36.5	78.0	41.7

*Individual value represents the final duration of time (sec) attending to novel objects in each 10 minute trial for each rat.

Appendix B6 Data for Trial 2 (T2) in the object recognition task for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
251	1	T2	93.2	82.8	50.0
252	1	T2	60.1	54.4	60.8
253	1	T2	70.6	56.0	48.9
254	1	T2	47.7	80.5	64.4
255	1	T2	41.8	69.0	67.5
256	1	T2	47.4	59.7	61.3
257	1	T2	37.7	53.1	55.2
258	1	T2	58.2	68.0	53.9
259	1	T2	75.9	63.2	82.7
260	1	T2	65.0	75.7	69.1
261	1	T2	56.3	63.5	60.6
262	1	T2	61.2	59.2	80.9
263	2	T2	73.2	31.0	44.3
264	2	T2	51.5	75.5	68.2
265	2	T2	50.2	66.6	23.4
266	2	T2	27.9	67.8	48.8
267	2	T2	68.1	75.8	79.6
268	2	T2	55.9	52.9	48.0
269	2	T2	27.1	64.3	51.9
270	2	T2	43.0	52.1	63.5
271	2	T2	56.0	59.5	49.8
272	2	T2	57.1	56.2	63.7
273	2	T2	79.8	68.6	44.8
274	2	T2	54.1	54.5	46.1

*Individual value represents the percentage of time each rat spent investigating the novel (N) from the familiar (F) object calculated according to the formula N ÷ (N + F) x 100 for each 10 minute trial.

Appendix B7 Data for Trial 2 (T2) in the object recognition task for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
137	1	T2	75.8	65.1	60.9
138	1	T2	55.5	70.1	84.3
139	1	T2	83.4	49.2	53.2
140	1	T2	61.3	82.2	39.9
141	1	T2	78.2	64.2	84.9
142	1	T2	66.4	62.5	80.8
143	1	T2	50.4	54.0	58.6
144	1	T2	49.2	80.1	70.6
145	1	T2	73.6	78.8	63.6
146	1	T2	68.2	72.8	72.8
147	1	T2	73.6	75.7	57.6
148	1	T2	52.5	59.3	65.2
149	2	T2	88.2	89.6	71.9
150	2	T2	55.8	71.7	40.3
151	2	T2	56.2	48.0	29.0
152	2	T2	46.4	21.8	67.5
153	2	T2	39.5	69.1	72.6
154	2	T2	67.0	38.0	59.0
155	2	T2	56.8	39.1	49.1
156	2	T2	49.5	37.9	60.4
157	2	T2	71.4	61.0	34.5
158	2	T2	71.5	48.5	77.3
159	2	T2	21.1	63.6	63.6
160	2	T2	58.1	56.3	51.7

*Individual value represents the percentage of time each rat spent investigating the novel (N) from the familiar (F) object calculated according to the formula N ÷ (N + F) x 100 for each 10 minute trial.

Appendix B8 Data for trial 2 (T2) in the object recognition task for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
57	1	T2	70.9	47.6	53.0
58	1	T2	65.7	46.0	76.3
59	1	T2	53.9	64.2	55.6
60	1	T2	53.3	53.4	82.7
61	1	T2	81.9	60.9	39.9
62	1	T2	63.7	48.1	71.4
63	1	T2	41.6	54.4	68.8
64	1	T2	44.4	58.8	64.7
65	1	T2	75.5	72.2	84.2
66	1	T2	94.1	54.4	73.7
67	1	T2	96.5	78.3	52.7
68	1	T2	53.3	61.9	77.6
69	2	T2	55.8	71.0	37.4
70	2	T2	55.3	60.3	41.8
71	2	T2	72.4	34.7	69.6
72	2	T2	24.3	44.8	85.5
73	2	T2	73.0	47.7	78.9
74	2	T2	49.8	42.8	67.5
75	2	T2	21.2	52.6	35.5
76	2	T2	61.6	75.0	53.4
77	2	T2	48.5	60.5	69.8
78	2	T2	48.5	60.5	69.8
79	2	T2	76.9	63.0	51.8
80	2	T2	68.6	45.1	69.8

*Individual value represents the percentage of time each rat spent investigating the novel (N) from the familiar (F) object calculated according to the formula N ÷ (N + F) x 100 for each 10 minute trial.

Appendix B9 Data for trial 1 (T1) locomotor activity for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
251	1	T1	265.9	354.4	277.1
252	1	T1	281.4	344.5	283.4
253	1	T1	330.1	275.2	338.6
254	1	T1	346.4	205.3	346.9
255	1	T1	241.3	350.6	352.5
256	1	T1	330.9	324.5	349.1
257	1	T1	310.6	284.8	341.9
258	1	T1	356.8	316.6	343.7
259	1	T1	357.2	321.1	303.2
260	1	T1	365.3	316.6	305.1
261	1	T1	311.1	313.0	350.4
262	1	T1	315.5	358.5	354.0
263	2	T1	303.5	401.9	290.0
264	2	T1	309.0	361.7	289.1
265	2	T1	365.0	293.6	411.9
266	2	T1	278.5	299.4	340.4
267	2	T1	361.4	336.9	370.0
268	2	T1	337.8	262.9	328.0
269	2	T1	331.1	298.9	363.1
271	2	T1	358.1	308.9	323.6
271	2	T1	345.9	292.5	306.6
272	2	T1	377.9	306.2	317.9
273	2	T1	289.9	320.3	354.1
274	2	T1	354.0	365.4	364.4

*Each value represents the total duration (sec) time each rat spent in locomotor activity for each 10 minute session.

Appendix B10 Data for trial 1 (T1) locomotor activity for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
137	1	T1	223.5	390.9	299.8
138	1	T1	306.4	407.9	299.2
139	1	T1	352.1	255.9	317.7
140	1	T1	301.9	240.5	360.0
141	1	T1	323.2	276.1	367.6
142	1	T1	323.2	308.1	353.9
143	1	T1	338.7	304.1	362.5
144	1	T1	310.7	277.1	373.3
145	1	T1	339.9	319.3	255.7
146	1	T1	432.0	363.4	372.0
147	1	T1	274.4	319.7	339.7
148	1	T1	329.4	335.6	386.1
149	2	T1	291.8	423.5	273.7
150	2	T1	267.4	403.5	329.6
151	2	T1	365.2	331.2	380.0
152	2	T1	329.9	327.6	362.3
153	2	T1	253.1	326.3	362.4
154	2	T1	345.3	318.0	381.4
155	2	T1	268.0	295.0	377.7
156	2	T1	337.9	290.4	372.9
157	2	T1	345.1	310.4	296.9
158	2	T1	406.6	365.8	339.1
159	2	T1	322.1	364.2	367.4
160	2	T1	354.3	362.7	360.0

*Each value represents the total duration (sec) time each rat spent in locomotor activity for each 10 minute session.

Appendix B11 Data for trial 1 (T1) locomotor activity for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
57	1	T1	313.2	350.8	285.2
58	1	T1	322.0	279.4	283.1
59	1	T1	312.1	332.0	314.3
60	1	T1	246.1	260.4	240.6
61	1	T1	269.2	277.9	272.2
62	1	T1	294.6	314.4	278.4
63	1	T1	334.4	313.0	290.0
64	1	T1	330.6	302.0	285.7
65	1	T1	353.1	346.7	312.0
66	1	T1	134.0	206.5	305.1
67	1	T1	167.4	299.9	297.5
68	1	T1	354.8	370.3	341.6
69	2	T1	273.3	286.5	292.2
70	2	T1	294.5	307.0	307.2
71	2	T1	333.9	344.3	306.0
72	2	T1	271.0	194.9	313.3
73	2	T1	254.6	252.9	217.5
74	2	T1	300.0	338.9	309.7
75	2	T1	241.4	282.1	319.3
76	2	T1	332.0	330.0	340.3
77	2	T1	266.4	250.5	226.8
78	2	T1	282.7	285.2	313.5
79	2	T1	271.2	318.3	327.0
80	2	T1	259.6	325.4	355.7

*Each value represents the total duration (sec) time each rat spent in locomotor activity for each 10 minute session.

Appendix B12 Data for trial 2 (T2) locomotor activity for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
251	1	T2	284.3	308.7	252.0
252	1	T2	323.9	365.6	257.9
253	1	T2	324.2	284.5	267.1
254	1	T2	346.2	329.5	304.5
255	1	T2	254.4	302.1	383.9
256	1	T2	326.1	359.6	341.7
257	1	T2	271.2	318.8	340.9
258	1	T2	335.7	320.7	387.2
259	1	T2	367.9	375.2	307.6
260	1	T2	355.7	341.4	300.3
261	1	T2	330.0	274.4	299.1
262	1	T2	309.3	354.7	301.2
263	2	T2	281.0	393.1	256.7
264	2	T2	296.4	341.1	338.1
265	2	T2	359.7	320.8	326.7
266	2	T2	303.7	273.6	292.7
267	2	T2	352.9	367.8	362.4
268	2	T2	297.8	355.1	305.9
269	2	T2	304.8	313.4	338.6
270	2	T2	309.1	328.5	347.4
271	2	T2	335.7	382.7	264.3
272	2	T2	366.6	323.9	298.9
273	2	T2	256.6	328.9	314.8
274	2	T2	334.0	318.4	361.7

*Each value represents the total duration (sec) time each rat spent in locomotor activity for each 10 minute session

Appendix B13 Data for trial 2 (T2) locomotor activity for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
137	1	T2	286.0	337.9	279.4
138	1	T2	347.2	367.9	291.4
139	1	T2	334.6	253.0	262.7
140	1	T2	326.9	318.4	293.6
141	1	T2	249.4	191.9	343.1
142	1	T2	236.6	296.0	300.3
143	1	T2	292.3	344.9	348.6
144	1	T2	281.9	350.2	342.4
145	1	T2	320.5	338.5	341.6
146	1	T2	377.5	336.1	320.7
147	1	T2	252.0	317.9	348.6
148	1	T2	310.9	350.2	354.6
149	2	T2	280.9	299.7	355.4
150	2	T2	287.6	290.5	295.5
151	2	T2	339.3	341.0	332.1
152	2	T2	324.8	342.1	352.2
153	2	T2	264.5	302.8	354.5
154	2	T2	309.8	354.9	282.5
155	2	T2	278.7	335.4	339.2
156	2	T2	320.8	282.2	376.6
157	2	T2	318.4	332.6	345.6
158	2	T2	383.7	335.6	351.9
159	2	T2	363.4	356.4	325.6
160	2	T2	336.1	388.7	388.1

*Each value represents the total duration (sec) time each rat spent in locomotor activity for each 10 minute session.

Appendix B14 Data for trial 2 (T2) locomotor activity for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Trial	2 h	6 h	48 h
57	1	T2	306.0	300.9	290.6
58	1	T2	315.4	322.3	267.7
59	1	T2	328.1	360.6	299.0
60	1	T2	227.0	250.1	276.9
61	1	T2	202.2	244.0	280.0
62	1	T2	268.3	271.0	293.7
63	1	T2	295.3	337.1	305.9
64	1	T2	300.9	304.9	332.7
65	1	T2	304.4	303.9	309.2
66	1	T2	81.9	294.0	261.0
67	1	T2	158.1	280.1	230.3
68	1	T2	326.5	329.6	325.0
69	2	T2	260.1	295.7	278.7
70	2	T2	279.1	247.4	305.0
71	2	T2	291.6	308.4	310.0
72	2	T2	205.3	168.2	260.0
73	2	T2	156.8	176.2	261.4
74	2	T2	301.8	306.7	355.5
75	2	T2	221.7	305.2	322.7
76	2	T2	260.0	326.6	326.4
77	2	T2	235.5	242.0	249.7
78	2	T2	245.8	303.6	294.7
79	2	T2	268.4	337.8	294.7
80	2	T2	240.2	312.1	318.9

*Each value represents the total duration (sec) time each rat spent in locomotor activity for each 10 minute session.

Appendix B15 Data (see column "Total") used to calculated the total social behaviour (Chapter 5) for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Sniffing	Following	Grooming	Mounting	Crawling under/over	Total
251	1	21.9	0.8	0	0	10	32.7
252	1	17.4	4.2	0	0	7.6	29.2
253	1	40.5	6.8	0	0.2	12	59.5
254	1	76.9	2.2	0.5	0.4	1	81
255	1	66.6	4.4	0	0	4.5	75.5
256	1	85.9	17.8	0	0	3.1	106.8
257	1	39.7	1.9	0	7.5	4.7	53.8
258	1	47.2	4.7	0	0	23.4	75.3
259	1	54.3	6.3	0	0	20.4	81
260	1	101.1	3.1	0	0.2	1.6	106
261	1	40.1	0.2	0	0	18.1	58.4
262	1	87.8	15.5	0	0	7.7	111
263	2	16.8	0.1	0	0	4.9	21.8
264	2	29.2	2.6	0	0	3.7	35.5
265	2	20.8	3.7	0	0	3.6	28.1
266	2	19.2	1	0	0	0.6	20.8
267	2	24.3	0.6	0	0	0.6	25.5
268	2	89.4	2.8	0	2.2	2.6	97
269	2	4.8	0.1	0	0	2.5	7.4
270	2	2.4	0.2	0	3.5	6.9	13
271	2	18.9	0.2	0	0	1.1	20.2
272	2	65.7	1.8	0	0	9.5	77
273	2	52.1	1.3	0	0.3	0.8	54.5
274	2	19.6	0.1	0	2	3.7	25.4

*Each value represents the cumulative duration (sec) of each social behaviour for each rat for each 10 minute session. These behaviours were then summed to obtain a total social behaviour score.

Appendix B16 Data (see column "Total") used to calculated the total social behaviour (Chapter 5) for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Sniffing	Following	Grooming	Mounting	Crawling under/over	Total
137	1	76.4	12.4	7.1	0	6	101.9
143	1	15.9	0	0	0	0	15.9
138	1	28.7	0	0	0	1.8	30.5
144	1	24.9	0	0	0	0	24.9
139	1	58.2	15.3	0	3.3	12.1	88.9
145	1	19.1	0.1	0	0	5.3	24.5
140	1	48.8	1.8	0	0	0.9	51.5
146	1	64.4	5.5	0	0	0	69.9
141	1	41.6	5.5	0	0	2.3	49.4
147	1	58.6	10.1	0	1.2	7.2	77.1
142	1	6.2	1.3	0	1.9	4.1	13.5
148	1	51	6.2	0	0	10.8	68
149	2	21.7	0.3	0	0.6	5.2	27.8
155	2	12.2	0.3	0	0	0.9	13.4
150	2	20.8	1.6	0	1.4	8.5	32.3
156	2	10.5	1.2	0	0	0.3	12
151	2	5.2	0.9	0	1.1	0.1	7.3
157	2	4.3	0.7	1	0.6	0.2	6.8
152	2	13.5	1.2	0	0	0.7	15.4
158	2	8.1	0.5	0	0.7	3.9	13.2
153	2	26.6	0.8	0	1	0.3	28.7
159	2	19.7	1	0	0	1.8	22.5
154	2	15.1	1.4	0	1.1	1	18.6
160	2	40.8	4.6	2	0	2.1	49.5

*Each value represents the cumulative duration (sec) of each social behaviour for each rat for each 10 minute session. These behaviours were then summed to obtain a total social behaviour score.

Appendix B17 Data (see column "Total") used to calculated the total social behaviour (Chapter 5) for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Sniffing	Following	Grooming	Mounting	Crawling under/over	Total
57	1	55.3	12.3	0	0	10.2	77.8
58	1	13.7	0.3	0	6.5	2.4	22.9
59	1	51.7	4	0	0	0.1	55.8
60	1	122.5	9	0	0.1	24.5	156.1
61	1	97.7	23.5	0	0	18.7	139.9
62	1	51.7	2.1	2	1.1	1	57.9
63	1	74.4	27.5	0	0.4	16	118.3
64	1	50.7	0.8	0	0	0.2	51.7
65	1	81.9	16.9	0	0	37.4	136.2
66	1	25.7	1	0	0.1	5.7	32.5
67	1	84.1	8.6	0	0	4	96.7
68	1	79.8	13.9	0	0	9	102.7
69	2	33.2	15.2	0	0	0	48.4
70	2	12.3	0.8	0	0	6.3	19.4
71	2	28.1	0.8	0	0.2	4.7	33.8
72	2	16.3	0.8	0	0	0	17.1
73	2	34.8	1	0	0	6.4	42.2
74	2	23.9	10	0	0	1.4	35.3
75	2	15.4	0.4	0	0	0.3	16.1
76	2	42.6	0.6	0	0	7.3	50.5
77	2	4.1	0.2	0	0	0	4.3
78	2	24.2	1.7	0	0	0.6	26.5
79	2	41.2	0.4	0	2.9	17.4	61.9
80	2	55.9	18.1	0	2.6	1.8	78.4

*Each value represents the cumulative duration (sec) of each social behaviour for each rat for each 10 minute session. These behaviours were then summed to obtain a total social behaviour score.

Appendix B18 Data used to analyse each social interaction behaviour inclusive of both non-aggressive (Chapter 5) and aggressive (Chapter 6) social behaviours for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Sniffing	Following	Grooming	Kicking	Mounting	Jumping on	Wrestling/ boxing	Crawling under/ over
251	1	21.9	0.8	0	0	0	0.5	58.5	10
252	1	17.4	4.2	0	0	0	6.7	92.3	7.6
253	1	40.5	6.8	0	0	0.2	3.2	30.1	12
254	1	76.9	2.2	0.5	0	0.4	14.7	25.1	1
255	1	66.6	4.4	0	0	0	4.4	23	4.5
256	1	85.9	17.8	0	0	0	2.9	37.1	3.1
257	1	39.7	1.9	0	0	7.5	5.1	67.2	4.7
258	1	47.2	4.7	0	0	0	7.7	100.5	23.4
259	1	54.3	6.3	0	0	0	2	25.1	20.4
260	1	101.1	3.1	0	0	0.2	11.1	28.5	1.6
261	1	40.1	0.2	0	0	0	5.3	16.3	18.1
262	1	87.8	15.5	0	0	0	0.7	35.5	7.7
263	2	16.8	0.1	0	0	0	0.6	23.1	4.9
264	2	29.2	2.6	0	0	0	0.2	26.1	3.7
265	2	20.8	3.7	0	0	0	3.9	81.2	3.6
266	2	19.2	1	0	0	0	0	0	0.6
267	2	24.3	0.6	0	0	0	2.9	12.9	0.6
268	2	89.4	2.8	0	0	2.2	7.4	0.6	2.6
269	2	4.8	0.1	0	0	0	2.4	58	2.5
270	2	2.4	0.2	0	0	3.5	4.3	38.5	6.9
271	2	18.9	0.2	0	0	0	0	39.6	1.1
272	2	65.7	1.8	0	0	0	0.8	0	9.5
273	2	52.1	1.3	0	0	0.3	12.1	37.8	0.8
274	2	19.6	0.1	0	0	2	4.7	1.8	3.7

Appendix B19 Data used to analyse each social interaction behaviour inclusive of both non-aggressive (Chapter 5) and aggressive (Chapter 6) social behaviours for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Sniffing	Following	Grooming	Kicking	Mounting	Jumping on	Wrestling/ boxing	Crawling under/ over
137	1	76.4	12.4	7.1	0	0	8	0	6
143	1	15.9	0	0	0	0	0.2	0	0
138	1	28.7	0	0	0	0	0	0	1.8
144	1	24.9	0	0	0	0	0	0	0
139	1	58.2	15.3	0	0	3.3	7.5	35.2	12.1
145	1	19.1	0.1	0	0	0	6.3	72.6	5.3
140	1	48.8	1.8	0	0	0	4.6	0.6	0.9
146	1	64.4	5.5	0	0	0	4.6	0	0
141	1	41.6	5.5	0	0	0	4	48.7	2.3
147	1	58.6	10.1	0	0	1.2	5.6	44.2	7.2
142	1	6.2	1.3	0	0.7	1.9	0	1.2	4.1
148	1	51	6.2	0	0	0	4.4	1.8	10.8
149	2	21.7	0.3	0	0	0.6	0.4	0	5.2
155	2	12.2	0.3	0	0	0	1.3	0	0.9
150	2	20.8	1.6	0	0	1.4	2.3	14.6	8.5
156	2	10.5	1.2	0	0	0	0	16	0.3
151	2	5.2	0.9	0	0	1.1	2.1	43.1	0.1
157	2	4.3	0.7	1	0	0.6	1.1	44.1	0.2
152	2	13.5	1.2	0	0	0	2.7	11.4	0.7
158	2	8.1	0.5	0	0.2	0.7	0	13.9	3.9
153	2	26.6	0.8	0	0	1	2.4	5.4	0.3
159	2	19.7	1	0	0	0	0.6	12.1	1.8
154	2	15.1	1.4	0	0	1.1	1.1	17.5	1
160	2	40.8	4.6	2	0	0	2	24.5	2.1

Appendix B20 Data used to analyse each social interaction behaviour inclusive of both non-aggressive (Chapter 5) and aggressive (Chapter 6) social behaviours for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Sniffing	Following	Grooming	Kicking	Mounting	Jumping on	Wrestling/ boxing	Crawling under/ over
57	1	55.3	12.3	0	0	0	1.8	0.2	10.2
58	1	13.7	0.3	0	0	6.5	4.9	17	2.4
59	1	51.7	4	0	0	0	1	0	0.1
60	1	122.5	9	0	0	0.1	0	0.1	24.5
61	1	97.7	23.5	0	0	0	8	3	18.7
62	1	51.7	2.1	2	0	1.1	1	0	1
63	1	74.4	27.5	0	0	0.4	6.5	1.2	16
64	1	50.7	0.8	0	0	0	2.7	35.5	0.2
65	1	81.9	16.9	0	0	0	0	0	37.4
66	1	25.7	1	0	0	0.1	1.4	0	5.7
67	1	84.1	8.6	0	0	0	3.6	0.9	4
68	1	79.8	13.9	0	0	0	0.1	0	9
69	2	33.2	15.2	0	0	0	0.4	0	0
70	2	12.3	0.8	0	0	0	0	0	6.3
71	2	28.1	0.8	0	0	0.2	0.1	0.5	4.7
72	2	16.3	0.8	0	0	0	0.2	0.2	0
73	2	34.8	1	0	0	0	0	0	6.4
74	2	23.9	10	0	0	0	0.3	0	1.4
75	2	15.4	0.4	0	0	0	0	0	0.3
76	2	42.6	0.6	0	0	0	0.8	0	7.3
77	2	4.1	0.2	0	0	0	0.2	1	0
78	2	24.2	1.7	0	0	0	1.9	0	0.6
79	2	41.2	0.4	0	0	2.9	0.5	0.2	17.4
80	2	55.9	18.1	0	0	2.6	0.1	0	1.8

Appendix B21 Data used to analyse emergence latency for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Emergence latency
253	1	45.4
252	1	2.9
251	1	27.1
262	1	62.3
260	1	12.2
259	1	10.1
254	1	49.5
255	1	8.5
261	1	29.7
257	1	0.7
256	1	1.1
258	1	6
269	2	67.7
266	2	5.6
274	2	27.1
271	2	3.1
267	2	69.2
264	2	18
273	2	10.6
270	2	30.6
268	2	99.2
263	2	89.5
272	2	2.4
265	2	60.8

Appendix B22 Data used to analyse emergence latency for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Emergence latency
139	1	9
155	2	12.2
138	1	37
152	2	36.6
137	1	10.8
160	2	18.7
148	1	3.7
157	2	1.2
146	1	0.7
153	2	2.1
145	1	8.6
150	2	5.1
140	1	6.6
159	2	6.4
141	1	5.2
156	2	4.8
147	1	7.7
154	2	7.4
143	1	73.2
149	2	21.1
142	1	1.5
158	2	1.5
144	1	4.1
151	2	1.9

Appendix B23 Data used to analyse emergence latency for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Emergence latency
59	1	9.7
75	2	13.3
58	1	21.6
72	2	8.8
57	1	21.1
80	2	13.8
68	1	6.6
77	2	19.5
66	1	15
73	2	4
65	1	5.1
70	2	8.2
60	1	13.5
79	2	18.9
61	1	7.7
76	2	4.2
67	1	16.4
74	2	17.5
63	1	10.4
69	2	17.4
62	1	7.9
78	2	10.3
64	1	2.6
71	2	21.6

Appendix B24 Data used to analyse emergence test behaviours for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Emergence frequency	Open field	Risk assessment	Rears	Line crosses	Hide box
253	1	5	203.1	14.1	0	29	61.8
252	1	4	246.2	0.7	0	52	35.4
251	1	2	230.3	1.4	0	65	53.9
262	1	4	144.4	18.8	0	26	131.9
260	1	5	224.1	6.6	0	87	54.1
259	1	4	228	0.8	0	77	52.7
254	1	5	210	8.3	0	64	69.1
255	1	6	212.5	0	0	40	65.8
261	1	10	164	0	0	28	109.7
257	1	2	243.1	0.7	0	64	42.9
256	1	4	232.8	0	0	75	52.2
258	1	3	226.4	3.8	0	68	60.1
269	2	2	216.9	20.6	0	19	73
266	2	4	227.3	8.3	0	57	53.4
274	2	2	180.5	14.9	0	56	86.7
271	2	4	219.5	0	0	90	51
267	2	4	183.4	15	0	22	105.5
264	2	5	227.9	8.5	0	59	60.7
273	2	4	216.4	1.6	0	78	62.9
270	2	4	211.1	12.7	0	67	58.5
268	2	8	180.3	1.4	0	38	104.6
263	2	7	161.8	5.7	0	37	121
272	2	3	253.2	0.2	0	99	38.4
265	2	8	212.3	1.9	0	63	75.8

Appendix B25 Data used to analyse emergence test behaviours for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Emergence frequency	Open field	Risk assessment	Rears	Line crosses	Hide box
139	1	3	219.3	1	0	77	51.6
138	1	3	211.5	8.4	0	67	70.7
137	1	6	232.4	5.9	0	59	55.1
148	1	3	221.8	4.2	0	72	67.2
146	1	4	243.7	0.6	0	96	27.6
145	1	3	240.8	4.5	0	67	49.4
140	1	5	249.5	1.1	0	83	40.9
141	1	10	227.5	0.6	0	88	60.2
147	1	4	241.6	3.5	0	74	44.9
143	1	3	190.9	34	0	41	88.2
142	1	4	254.1	0	0	111	25.9
144	1	6	216.9	1	0	67	67.1
155	2	5	269.3	0.4	0	59	19.4
152	2	4	206	4	0	74	70.6
160	2	5	263.7	6.2	0	42	28.4
157	2	3	243.4	1.9	0	54	35.4
153	2	3	274.5	0	0	100	16.1
150	2	3	219.7	1.6	0	68	51.7
159	2	6	262.6	1.1	0	78	26
156	2	3	270.7	0	0	79	21.7
154	2	5	262.8	0.3	0	60	23.9
149	2	3	184.4	3.4	0	73	62.3
158	2	5	264.7	0.1	0	83	26.1
151	2	6	212.9	0.6	0	78	62.9

Appendix B26 Data used to analyse emergence test behaviours for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Rat	Group	Emergence frequency	Open field	Risk assessment	Rears	Line crosses	Hide box
59	1	4	252.5	0.3	0	93	35.5
58	1	8	184	2.2	0	71	89.8
57	1	3	204.8	1.1	0	95	44.2
68	1	7	200.3	0.4	0	74	34.5
66	1	6	210.6	1.9	0	77	69.7
65	1	5	246.5	0.8	0	88	41.4
60	1	5	216.7	4.5	0	71	63.7
61	1	4	239.5	2.4	0	66	52.2
67	1	7	221.6	6.6	0	67	71
63	1	5	221	1.1	0	60	67.2
62	1	6	224.1	1.7	0	79	67.2
64	1	4	230.6	0	0	67	58.8
75	2	3	214.1	0	0	73	61.9
72	2	5	237.4	0.2	0	94	43.9
80	2	4	207.6	0	0	73	56.7
77	2	4	212.4	5.2	0	76	58.3
73	2	4	129.5	1.4	0	42	66.4
70	2	5	221	2.2	0	81	70
79	2	4	225.7	8.6	0	60	64.7
76	2	7	215	9.8	0	56	76.3
74	2	6	203.4	2.4	0	76	77.5
69	2	7	200.3	0.7	0	76	82.9
78	2	4	239.7	1.8	0	72	49.9
71	2	4	232.4	0.8	0	53	62

Appendix B27 Data used to compare Fos for perinatal vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Peri Rat	Group	Cort insular	Med CPU	Cort piriform	NA core	NA shell	Lat Sep ven	BNST ld	Amy bas nuc	Amy cen nuc	Amy med nuc	Peri gray dor	Peri gray lat	Peri gray vent	Hipp CA1	Hipp CA3
251	1	0	0	1	0	0	2	0	0	0	1	0	0	0	0	0
252	1	4	3	54	0	2	18	3	1	2	7	9	2	1	0	0
253	1	1	1	55	0	0	0	0	7	18	22	11	15	2	0	0
254	1	1	0	34	0	0	6	0	4	5	5	10	15	17	0	2
257	1	0	0	6	0	0	1	0	4	4	3	1	2	1	0	1
258	1	2	3	51	0	0	5	0	6	8	5	13	9	8	0	1
259	1	0	0	18	0	0	9	0	3	11	12	9	13	17	0	0
260	1	0	2	24	0	1	3	0	3	6	1	3	3	5	0	0
263	2	0	0	9	0	0	1	0	1	3	1	2	1	1	0	0
264	2	4	2	50	0	1	9	0	0	0	5	1	2	19	0	0
265	2	0	1	15	0	1	6	1	0	2	3	3	6	3	0	0
266	2	1	11	84	6	1	18	0	6	5	16	7	2	8	0	0
269	2	0	5	55	0	0	29	0	4	9	11	10	15	23	1	1
270	2	0	0	17	0	0	2	0	0	0	8	2	0	12	0	0
271	2	3	4	46	2	5	7	0	8	5	15	1	8	10	2	2
272	2	1	8	20	0	0	6	0	1	1	10	1	5	0	0	1

Appendix B28 Data used to compare Fos for adolescent vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Adol Rat	Group	Cort insular	Med CPU	Cort piriform	NA core	NA shell	Lat Sep ven	BNST ld	Amy bas nuc	Amy cen nuc	Amy med nuc	Peri gray dor	Peri gray lat	Peri gray vent	Hipp CA1	Hipp CA3
137	1	1	0	4	1	0	1	1	0	3	1	0	0	0	0	0
138	1	0	2	30	1	1	7	7	5	0	1	2	3	5	0	0
139	1	0	0	13	0	0	2	2	3	0	9	0	0	0	0	0
140	1	0	0	1	0	0	1	1	0	0	0	0	0	9	0	0
143	1	1	1	12	1	0	3	0	1	0	9	0	0	2	0	0
144	1	0	0	8	0	0	3	0	0	0	0	1	0	10	0	0
145	1	0	0	2	0	0	4	0	2	1	9	6	0	5	0	0
146	1	0	0	5	0	0	11	0	0	4	3	4	0	1	0	0
149	2	0	0	1	0	0	3	0	0	1	1	0	0	10	0	0
150	2	0	2	70	2	0	7	7	5	1	1	3	1	4	0	0
151	2	0	0	10	0	1	5	0	0	1	2	1	1	0	0	0
152	2	1	2	5	0	0	2	0	0	5	17	3	0	12	0	1
155	2	0	0	0	1	0	2	1	3	0	0	0	0	1	0	0
156	2	0	0	5	0	0	2	0	2	2	6	3	0	15	0	0
157	2	2	0	3	0	1	3	0	0	0	1	2	1	5	0	0
158	2	0	0	2	0	0	0	1	0	0	0	2	0	0	0	0

Appendix B29 Data used to compare Fos for adult vehicle (group= 1) and CP 55,940 (group= 2) treated rats

Adult Rat	Group	Cort insular	Med CPU	Cort piriform	NA core	NA shell	Lat Sep ven	BNST ld	Amy bas nuc	Amy cen nuc	Amy med nuc	Peri gray dor	Peri gray lat	Peri gray vent	Hipp CA1	Hipp CA3
57	1	0	0	2	0	3	1	0	0	0	3	5	1	2	0	0
58	1	5	5	64	1	10	10	1	16	7	0	0	1	9	0	0
59	1	0	0	8	0	0	0	4	0	0	1	0	0	3	0	0
60	1	2	0	20	0	0	1	0	2	3	5	2	0	0	0	0
64	1	8	5	60	3	13	4	0	3	3	10	1	2	13	2	0
65	1	1	0	10	0	0	0	0	0	2	1	0	0	0	1	0
66	1	1	0	9	0	3	0	0	2	0	1	10	0	1	0	0
67	1	1	0	12	0	1	0	0	0	1	2	1	0	1	0	0
69	2	0	0	6	0	0	2	0	0	6	5	1	2	7	0	0
70	2	0	0	16	0	0	3	0	0	4	5	1	0	4	0	1
71	2	0	0	15	0	0	0	0	0	1	2	1	0	0	1	0
72	2	0	0	23	0	1	4	0	1	5	4	1	1	0	0	0
75	2	6	1	11	4	3	0	0	2	1	3	2	0	7	1	0
76	2	1	10	48	0	8	4	0	5	7	12	1	1	0	0	0
77	2	3	0	20	0	0	0	0	0	2	4	0	0	0	0	0
78	2	0	2	16	4	5	4	0	0	0	6	2	1	4	0	0

FOREWORD TO APPENDIX C

The following article was published in the *Journal of Psychopharmacology*, Issue 18(4), pages 503-509, 2004. Malini E. Singh, a PhD colleague; Paul E. Mallet, my primary PhD supervisor; and Dr. Iain S. McGregor, my co-supervisor appear as co-authors on the paper, which is titled "Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats". This research was supported by an ARC Discovery Grant, a UNERA, and an Australian Postgraduate Award (APA). Although a large part of this research took place during PhD candidature, a portion constituted partial requirement of the MPsych (Clinical), therefore, this publication is presented here for the reader's interest only.

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Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats

Melanie O'Shea *School of Psychology, University of New England, Armidale, New South Wales, Australia.*
Malini E. Singh *School of Psychology, University of New England, Armidale, New South Wales, Australia.*
Iain S. McGregor *School of Psychology, Sydney University, New South Wales, Australia.*
Paul E. Mallet *School of Psychology, University of New England, Armidale, New South Wales, Australia.*

Abstract

Although many studies have examined the acute behavioural effects of cannabinoids in rodents, few have examined the lasting effects of cannabinoids at different developmental ages. This study compared lasting effects of cannabinoid exposure occurring in adolescence to that occurring in early adulthood. Forty, 30-day old (adolescent) and 18, 56-day old (adult) female albino Wistar rats were injected with vehicle or incremental doses of the cannabinoid receptor agonist (–)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl) cyclohexanol (CP 55,940) once per day for 21 consecutive days (150, 200 and 300 μg/kg i.p. for 3, 8 and 10 days, respectively). Following a 21-day drug-free period, working memory was assessed using an object recognition task. Locomotor activity was also measured in the object recognition apparatus via a ceiling-mounted passive infrared sensor. Three days later, anxiety was assessed using a social interaction test. In the object recognition task, significantly poorer working memory was observed in the adolescent but not adult CP 55,940-treated rats. Adolescent, but not adult CP 55,940-treated rats, also exhibited a significant decrease in social interaction with a novel conspecific. These results suggest that chronic exposure to a cannabinoid receptor agonist well after the immediate postnatal period, but before reaching sexual maturity, can lead to increased anxiety and a lasting impairment of working memory.

Keywords

adolescent, anxiety, cannabinoid, CP 55,940, memory, object recognition, rat, social interaction

Introduction

Cannabis sativa has been used for thousands of years for both recreational and medical purposes but, despite this long history, very little is known about the long-lasting neurobehavioural effects of chronic cannabis use. The residual effects of cannabinoids, defined as the effects that persist long after the drug has left the central nervous system (CNS) (Pope *et al.*, 1995), have received only sparse research interest. In particular, the effects of cannabis initiation occurring in and around the adolescent period remains relatively unknown. Human cannabis use is commonly initiated in adolescence (Scallet, 1991), which coincides with major neuronal changes in the CNS (Ehrenreich *et al.*, 1999). Furthermore, in recent years, the age of initiation of cannabis use is becoming earlier in life. For example, a survey conducted in 1998 found that over 78% of adolescents had reported cannabis initiation at 14 years or younger compared to previous findings of 64% in 1992 (McCreary Centre Society, 1999). It is therefore of interest to determine whether adolescent cannabis use can produce lasting effects on cognitive function and emotion.

In the rat, adolescence can be defined as the period just before reaching sexual maturity (6–8 weeks; Fallon, 1995). Major changes in neuronal structure occur at this age, and the administration of cannabinoids at this time may produce marked changes in neuronal function (Rodríguez de Fonseca *et al.*, 1991). A few studies on rats corresponding to the same age (30–40 days old) have addressed the residual effects of cannabinoids on learning (Fehr *et al.*, 1976; Stiglick and Kalant, 1982, 1983). In these studies, varying doses of Δ^9-tetrahydrocannabinol (THC) were administered to 30-day old rats for 1–6 months, followed by a

Corresponding author: Paul E. Mallet, School of Psychology, University of New England, Armidale NSW 2351, Australia. *Email*: paul.mallet@une.edu.au

drug-free period of 1–2 months. Impairments on radial arm maze (note that this is a test of memory as well as learning) and motor coordination tasks were observed in rats treated with high doses for 6 months. The same investigators (Stiglick and Kalant, 1985) aimed to determine whether age at exposure could be a key determinant of these residual deficits. THC was administered to 70-day old adult rats for 3 months. After a 1–4 month drug-free period, no residual deficits were evident.

The possibility that human adolescents may be particularly vulnerable to adverse effects of cannabis is a matter of some recent speculation (Solowij and Grenyer, 2002). Although few human studies have specifically addressed this issue, there is some evidence that exposure during adolescence may lead to lasting deficits in attention (Ehrenreich *et al.*, 1999) and working memory (Schwartz *et al.*, 1989).

In humans, one of the most commonly reported effects of cannabinoid administration is an acute impairment of working memory (Miller, 1984). In animals, memory is impaired by the acute administration of THC, the endogenous cannabinoid anandamide (Compton *et al.*, 1996; Mallet and Beninger, 1996), or synthetic cannabinoids including (–)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl) cyclohexanol (CP 55,940) and WIN 55,212-2 (Lichtman *et al.*, 1995). A second commonly reported outcome of acute cannabis intoxication in humans is increased anxiety (Thomas, 1996). Frequent use has also been found to result in an increase in symptoms of anxiety (Patton *et al.*, 2002). In animals, these same anxiogenic effects are found by administering THC and other cannabinoids such as cannabinol (van Ree *et al.*, 1984), HU-210 (Giuliani *et al.*, 2000) and CP 55,940 (Arevalo *et al.*, 2001; Marin *et al.*, 2002). Some evidence of residual anxiety after discontinued administration has also been found (Ferrari *et al.*, 1999; Giuliani *et al.*, 2000).

The aim of the current study was to assess the possible lasting effects of chronic cannabinoid exposure on working memory and anxiety in adolescent and adult rats, using the synthetic cannabinoid CP 55,940. CP 55,940 produces behavioural and physiological effects analogous to THC including analgesia, catalepsy and hypothermia, which are similar in profile and time-course (Little *et al.*, 1988).

The object recognition task (Ennaceur and Delacour, 1988) was chosen to assess working memory because it has been found to be sensitive to both memory-enhancing (Ennaceur *et al.*, 1989), and memory-impairing treatments (Ennaceur *et al.*, 1997). Working memory is defined here as the immediate retention of information needed to respond to a current task or activity (Honig, 1978). The object recognition task is considered to be a test of 'pure' working memory because it has no reference memory component such as rule learning, and does not require the use of positive or negative reinforcers, such as food or electric shock (Ennaceur and Delacour, 1988). The task takes advantage of the rats' innate tendency to explore novel rather than familiar objects. A reduced tendency to prefer novel over familiar objects is indicative of working memory dysfunction. The task traditionally consists of two trials with intervening delays. Preference for the novel object relative to the familiar object typically decreases as the delays increase. The measurement of locomotor activity was introduced as an adjunct to this task to determine whether drug exposure results in long-term alterations in physical performance. Anxiety was assessed using the social interaction test (File, 1980), which involves measuring the interactions between a treated rat and an unfamiliar conspecific. The social interaction test has been well validated using a variety of anxiolytic (File *et al.*, 2001) and anxiogenic drugs (Irvine *et al.*, 2001) and has been recently used by our group to highlight residual anxiogenic effects of the popular recreational drug MDMA ('Ecstasy') (Morley *et al.*, 2001).

Materials and methods

Subjects

Fifty-eight female Wistar rats were used. The adolescent group (30 days old) comprised 20 drug-treated rats and 20 vehicle-treated rats. The adult group (56 days old) consisted of nine drug-treated rats and nine vehicle controls. Female rats were used because a previous study in humans found a larger association between cannabis use and anxiety in females compared to males (Patton *et al.*, 2002). Animals had access to food and water *ad libitum* and were group-housed in a temperature and humidity controlled colony room maintained on a 12 : 12 hour light/dark cycle.

Drug preparation and administration

CP 55,940 (Tocris Cookson, Avonmouth, UK) was dissolved in a vehicle containing 15 µl Tween 80 (polyoxyethylene sorbitan monooleate, ICN Biochemicals, Seven Hills, NSW, Australia), per 2 ml physiological saline. All injections were administered intraperitoneally in a volume of 1 ml/kg body weight. Rats in the drug-treated group received increasing doses of CP 55,940 for 21 consecutive days (150, 200 and 300 µg/kg for 3, 8 and 10 days, respectively), while the control group received similar exposure to the drug's vehicle. These moderate to high doses were chosen to be within the range known to produce behavioural effects in rats. Incrementally larger doses were used to counteract the development of drug tolerance because immature rats tend to develop tolerance to cannabinoids at a faster rate than mature rats (Barnes and Fried, 1974).

Apparatus and procedure

The Object Recognition Task The experimental chamber was a clear Perspex box (610 × 260 × 400 mm). Experiments were run under low light conditions. Each trial was videotaped using a black and white CCD camera with infrared illumination. Locomotor activity was measured by a passive infrared sensor (Quantum passive infrared motion sensor, NESS Security Products, Sydney, Australia, part no. 890-087-2) connected to a computer with custom software to detect and record time spent in motion. A 10-µF capacitor located near LK2 of the printed circuit board of the sensor was replaced with a 0.1-µF capacitor serving to alter the sensor alarm period from 5 s to approximately 50 ms.

Objects used included coffee mugs, tin cans, plastic bottles, rice bowls, red plastic boxes and tubs of hair gel. A pilot study found

this particular object set to elicit similar baseline rates of investigation. To eliminate any possible influence of olfactory cues, objects existed in triplicate such that two of the objects could be used in the first trial and the remaining object was used in the second trial. Objects were washed with Pyroneg (Johnson Diversey, Smithfield, NSW, Australia) before each trial, and the experimental chamber floor and walls were wiped between trials with a 1 : 10 vinegar–water solution. The assignment of objects used in any given trial was counterbalanced such that object combinations were distributed equally across groups.

Rats were habituated to the experimental chamber for two non-consecutive 2-min periods to reduce experimental chamber novelty. Formal testing began the next day. In the first trial (T_1), each rat was presented with two identical objects for 10 min. The aim of this trial was simply to provide an opportunity for the rats to explore two similar copies of an object. During the second trial (T_2), which occurred either 2 or 6 h later, the rats were again presented with two objects for 10 min. This time one object was novel, and the other was a triplicate of the original object presented in T_1. All rats were tested twice such that they experienced both delays between T_1 and T_2. In half the rats, the 2-h delay occurred first; in the other half, the 6-h delay occurred first. Testing in the second delay condition took place on the day after the first delay condition. The time spent exploring the objects during T_1 and T_2 were videorecorded. Object exploration was said to occur when the rat's snout was placed within 2 cm of the object. Climbing on or sitting on the object was not recorded. An observer blind to the group allocations manually scored the video recordings of each trial using the software package ODLog (Macropod Software, 2001; www.macropodsoftware.com).

The Social Interaction Test The experimental chamber was a rectangular box constructed of clear glass (620 × 300 × 360 mm), dimly lit by a floor lamp (60 W) located 1 m away from the box. On the day following social interaction testing, rats were habituated to the chamber for two non-consecutive 2-min periods. Testing began the next day, and involved the random pairing of each experimental rat with an untreated 'stimulus' rat for 10 min. Each trial was videotaped using a black and white CCD camera with infrared illumination. Subsequent behavioural analysis involved manually scoring the video recorded trials using ODLog software. Only the behaviour of the experimental rats was examined. Scored behaviours included sniffing, following, wrestling/boxing and grooming.

Statistical analysis

Object recognition The time spent exploring objects during T_1 was calculated by summing the time spent exploring each identical object to produce a single score. These values were then compared using two (one for each age group) mixed design (treatment × delay) analysis of variance (ANOVA) with repeated measures on the delay factor. A three-way (age × treatment × delay) ANOVA with repeated measures on the delay factor was also used to compare treatments at each age group.

The percentage of time spent investigating the novel object in T_2 was calculated according to the formula $N/(N + F) \times 100$, where N and F represented time spent investigating the novel and familiar objects, respectively. These values were then analysed using the same tests described for the T_1 data.

Locomotor activity Time spent in motion was recorded during all sessions. These values were then compared across experimental conditions using two age × treatment ANOVAs and one age × treatment × delay ANOVA as described previously for object recognition data.

Social interaction For each rat, the amount of time spent sniffing, following, wrestling/boxing and grooming were summed to produce a single social interaction score. A two-way ANOVA (age × treatment) was used to compare the social interaction between adolescent and adult groups. Separate t-tests were used to compare treatments at each age group.

Where the ANOVA assumptions were not met, randomization tests of scores were conducted using NPFact version 1.0. In all cases, the randomization tests supported the ANOVA findings. Thus, for ease of interpretation only, the ANOVA results have been presented. All ANOVAs were conducted using SPSS 11.0.2 (Chicago, Illinois, USA).

Results

Object recognition

Trial 1 In the adolescent rats, a mixed design ANOVA (treatment × delay) with repeated measures on the second factor revealed that the main effect of treatment [$F(1,38)$, $p < 1.0$] and the treatment by delay interaction [$F(1,38)$, $p < 1.0$] were not significant, whereas the delay main effect was significant [$F(1,38) = 5.47$, $p < 0.05$] (Fig. 1A). Within the adult groups, the main effect of treatment [$F(1,16)$, $p < 1.0$], the delay main effect [$F(1,16) < 1.0$] and the treatment by delay interaction [$F(1,16)$, $p < 1.0$] were not significant (Fig. 1B).

The three-way ANOVA (age × treatment × delay) revealed no significant main effects for age [$F(1,54)$, $p < 1.0$], treatment [$F(1,54)$, $p < 1.0$] or delay [$F(1,54) = 2.44$, $p > 0.05$]. The age × treatment–delay interaction [$F(1,54)$, $p < 1.0$], the age–treatment interaction [$F(1,54)$, $p < 1.0$] and the age–delay interaction [$F(1,54) = 1.19$, $p > 0.05$] were not significant.

Trial 2 Within adolescent treatment groups, the preference for novel over familiar objects was lower in the CP 55,940-treated group compared to vehicle controls. A mixed design (treatment × delay) ANOVA with repeated measures on delay revealed that the main effect of treatment was significant [$F(1,38) = 8.23$, $p < 0.01$]. However, the delay main effect [$F(1,38)$, $p < 1.0$] and the treatment by delay interaction [$F(1,38)$, $p < 1.0$] were not significant, suggesting that the delays had little effect on working memory (Fig. 2A). Within adult treatment groups, the main effect of treatment [$F(1,16)$, $p < 1.0$], the main effect of delay [$F(1,16)$, $p < 1.0$] and the treatment by delay interaction [$F(1,16)$, $p < 1.0$] were not significant (Fig. 2, B).

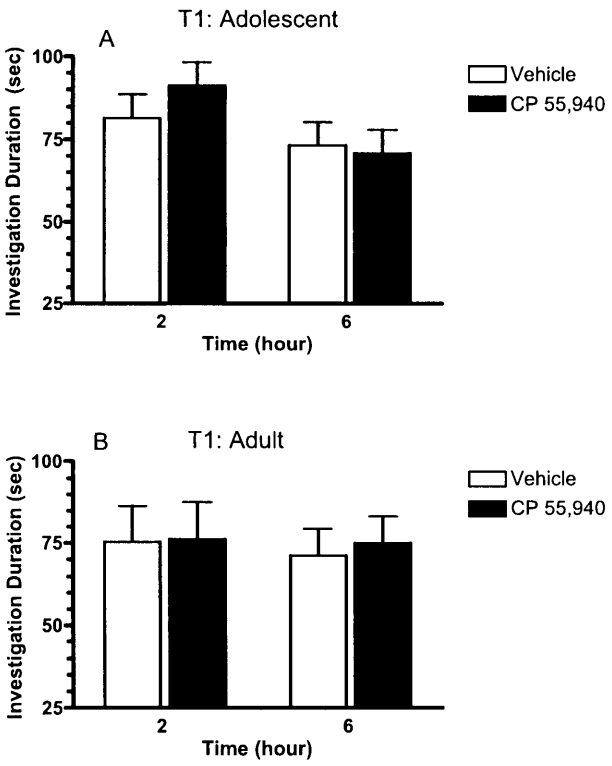

Figure 1 Object recognition: time (s) spent exploring identical objects in trial 1 (T_1) for adolescent (A) and adult (B) rats (n = 40 and 18, respectively) 2 or 6 h before the recognition test. Rats in half of each age group received 21 daily injections of either vehicle or CP 55,940 ending 22 days before testing

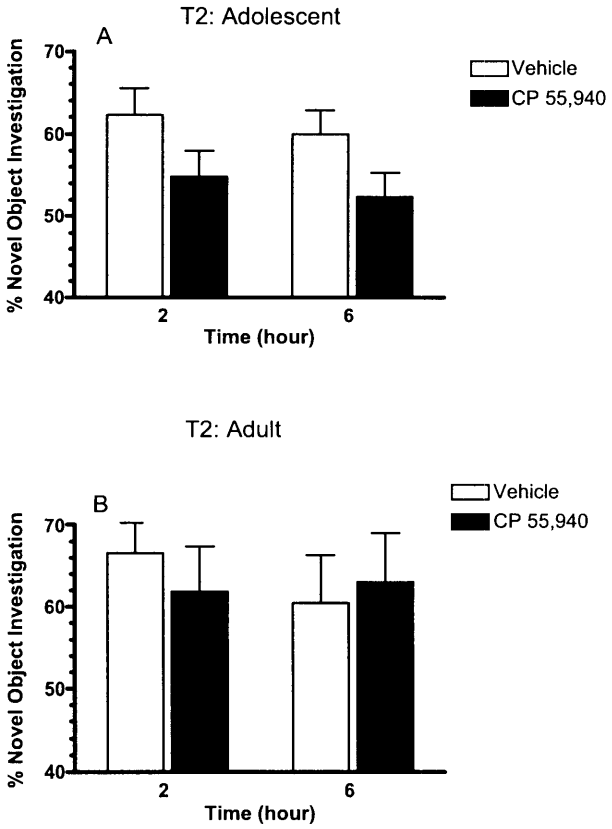

Figure 2 Object recognition: percentage of time investigating the novel object during T_2 for adolescent (A) and adult rats. The recognition test occurred either 2 or 6 h following T_1. Rats in half of each age group received 21 daily injections of either vehicle or CP 55,940 ending 22 days before testing

A three-way ANOVA (age × treatment × delay) revealed that the main effect of age was significant [$F(1,54) = 5.12$, $p < 0.05$]. The main effect of treatment [$F(1,54) = 3.00$, $p > 0.05$] and delay [$F(1,54)$, $p < 1.0$] were not significant. The age × treatment × delay interaction [$F(1,54)$, $p < 1.0$], the age × treatment interaction [$F(1,54) = 1.74$, $p > 0.05$] and the age × delay interaction [$F(1,54)$, $p < 1.0$] were not significant.

Locomotor activity

Trial 1 Locomotor activity did not differ across delays or treatments during T_1 in the adolescent rats. At the 2-h delay the mean ± SEM was 350.8 ± 34.9 and 351.4 ± 34.9 for vehicle- and CP 55,940-treated rats, respectively. At the 6-h delay values were 278.2 ± 29.6 and 357.9 ± 29.6. A mixed design (treatment × delay) ANOVA with repeated measures on delay revealed that the main effect of treatment [$F(1,38)$, $p = 1.0$], the main effect of delay [$F(1,38) = 2.25$, $p > 0.05$] and the treatment by delay interaction [$F(1,38) = 3.23$, $p > 0.05$] were not significant. Locomotor activity also did not differ across delays or treatments during T_1 in the adult rats. At the 2-h delay the mean ± SEM was 300.1 ± 9.9 and 298.5 ± 9.9 for vehicle- and CP 55,940-treated rats, respectively. At the 6-h delay these values were 273.7 ± 9.5 and 286.6 ± 9.5, respectively. ANOVA revealed that the main effect of treatment [$F(1,16)$, $p < 1.0$], the main effect of delay [$F(1,16) = 3.15$, $p > 0.05$] and the treatment by delay interaction [$F(1,16)$, $p < 1.0$] were not significant.

A three-way ANOVA (age × treatment × delay) revealed that the main effect of age [$F(1,54) = 2.19$, $p > 0.05$], the main effect of treatment [$F(1,54)$, $p < 1.0$] and the delay main effect [$F(1,54) = 2.37$, $p > 0.05$] were not significant. The age × treatment × delay interaction [$F(1,54)$, $p < 1.0$], the age × treatment interaction [$F(1,54)$, $p < 1.0$] and the age × delay interaction [$F(1,54)$, $p < 1.0$] were not significant.

Trial 2

Locomotor activity did not differ across delays or treatments during T_2 in the adolescent rats. At the 2-h delay, the mean ± SEM was 325.9 ± 36.9 and 315.4 ± 36.9 for vehicle- and CP 55,940-treated rats, respectively. At the 6-h delay, values were 342.4 ± 38.2 and

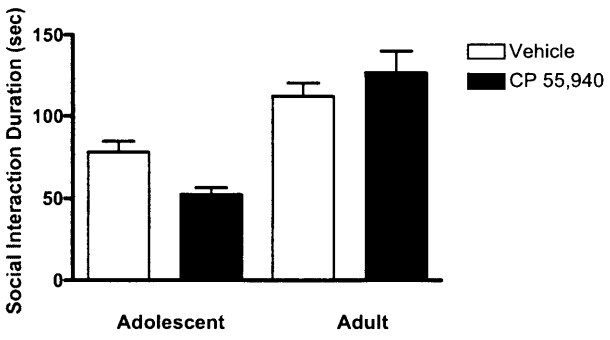

Figure 3 Social interaction: time (s) spent in social interaction for adolescent (n = 40) and adult (n = 18) rats. Rats in half of each age group received 21 daily injections of either vehicle or CP 55,940 ending 23 days before testing

347.6 ± 38.2. A mixed design (treatment × delay) ANOVA with repeated measures on delay revealed that the main effect of treatment [$F(1,38)$, $p < 1.0$], the main effect of delay [$F(2,38) = 1.17$, $p > 0.05$] and the treatment by delay interaction [$F(1,38)$, $p < 1.0$] were not significant. Similarly, locomotor activity did not differ across delays or treatments during T_2 in the adult rats. At the 2-h delay, the mean ± SEM was 280.4 ± 18.3 and 255.9 ± 18.3 for vehicle- and CP 55,940-treated rats. At the 6-h delay, these values were 293.4 ± 11.7 and 291.6 ± 11.7, respectively. ANOVA showed that the main effect of treatment [$F(1,16)$, $p < 1.0$], main effect of delay [$F(2,16) = 2.16$, $p > 0.05$] and treatment by delay interaction [$F(2,16)$, $p < 1.0$] were not significant.

A three-way ANOVA (age × treatment × delay) revealed that the main effect of age [$F(1,54)$, 2.07, $p > 0.05$], main effect of treatment [$F(1,54)$, $p < 1.0$] and delay main effect, [$F(1,54) = 1.87$, $p > 0.05$] were not significant. The age × treatment × delay interaction [$F(1,54)$, $p < 1.0$], age × treatment interaction [$F(1,54)$, $p < 1.0$] and age × delay interaction [$F(1,54)$, $p < 1.0$] were not significant.

Social interaction

An independent samples t-test used to compare the social interaction of the adolescent rats alone revealed that the CP 55,940-treated rats showed significantly less social interaction than the vehicle-treated group [$t(38) = 3.36$, $p < 0.05$] (Fig. 3). In adult rats, no significant difference in social interaction between vehicle and drug-treated groups was found [$t(16) < 1.0$] (Fig. 3).

A two-way ANOVA (age × treatment) comparing the social interaction between adolescent and adult groups revealed a significant main effect of age [$F(1,54) = 50.37$, $p < 0.001$]. The age × treatment interaction was also significant [$F(1,54)$] = 6.74, $p < 0.05$], suggesting that the adolescent rats exposed to CP 55,940 showed decreased social interaction compared to the adult groups. The treatment main effect was not significant [$F(1,54)$], $p < 1.0$].

Discussion

The results suggest that adolescent, but not adult rats treated with CP 55,940 showed reduced preference for a novel object over a familiar object relative to control animals at both delay intervals, suggesting that working memory was impaired. Locomotor activity during the object recognition task was not affected by CP 55,940 pre-treatment, suggesting that the results of the object recognition task cannot be attributed to a locomotor impairment or an overall lack of exploration.

The results of the social interaction test revealed that repeated pre-exposure to CP 55,940 significantly reduced social interaction compared to vehicle-treated rats in the adolescent rats, but not in the adult rats. Similar to the object recognition experiment, the results indicate that immature rats may incur lasting behavioural deficits from cannabinoid exposure, reflecting a residual effect of such exposure long after the drug has left the CNS.

The results of the object recognition experiment are in agreement with previous reports that cannabinoid exposure in immature (30–40 days old) but not mature rats (70 days old) impairs radial arm maze performance (Fehr *et al.*, 1976; Stiglick and Kalant, 1982, 1983). The present results also agree with findings of a human study on age-related cannabis exposure (Ehrenreich *et al.*, 1999), which assessed visual scanning along with other attentional functions in adult cannabis users whom had either been early (between ages 12–15 years) or late onset users (> 15 years). The results showed that early onset cannabis users had attention deficits specific to visual scanning, whereas late onset users did not. Another human study (Schwartz *et al.*, 1989) found that cannabis-using adolescents maintained working memory deficits when assessed up to 6 weeks after the last drug administration. A previous review (Scallet, 1991) also supported the existence of age-related residual effects by suggesting that lasting neurotoxic effects of THC appeared specific to young rats (40 days old or less), when exposure was chronic (> 90 days; 8–10% of the life span of a rat). At the time of the review, no other studies had demonstrated residual effects with shorter periods of exposure. However, in the current study, it was found that exposure for a mere 21 days (approximately 2% of a rat's life span) was sufficient to produce significant and lasting working memory deficits and increased anxiety.

To our knowledge, the present study is the first experiment to demonstrate residual anxiogenesis in younger rats resulting from prior exposure to CP 55,940. Recent studies have found evidence of a residual increase in anxiety in young adult rats chronically exposed to the cannabinoid receptor agonist HU-210 (Ferrari *et al.*, 1999; Giuliani *et al.*, 2000). In these studies, an increase in vocalizations and a heightened emotional response to novel environments were observed up to 7 days following exposure to the highest dose (100 µg/kg) of HU-210. It is not clear why CP 55,940 exposure did not produce a residual increase in anxiety in adult rats in the present study; however, methodological differences may account for these discrepant findings. For example, a different cannabinoid receptor agonist was used, and the drug-free period was considerably longer in our study.

Despite the interesting and novel results in the present study, there were also a few unexpected findings. First, baseline social interaction was lower in adolescent treatment groups compared to adults. This finding may be related to an age-related difference in the response to mild chronic injection stress. Thus, chronic intraperitoneal injections (even saline) can induce mild stress (Jaskiw *et al.*, 1990). Although both adolescent and adult control rats experienced similar vehicle injections, saline-treated adolescent rats exposed to mild stress are more anxious in a similar social test situation compared to adults rats (Spear, 2000; Varlinskaya and Spear, 2004). Furthermore, previous studies on early life cannabinoid exposure (Navarro *et al.*, 1994, 1996) indicate sexually dimorphic differences between male and female rats, perhaps explaining the lower rates of social interaction in females.

Another unusual finding was the significant effect of delay on investigation time during T_1 in the object recognition task. This result is difficult to interpret because delays were counterbalanced across testing days, and object investigation during T_1 was measured before the occurrence of any delays. We have not found a significant effect of delay during T_1 in any of our other work using this task and believe this finding can simply be attributed to Type 1 error. It is also not clear why the delay interval used had no significant effect on T_2 performance; however, it is possible that the 2 h and 6 h delays used were too similar in duration. The inclusions of a much longer delay interval would most likely have resulted in a significant effect of delay.

Sex differences in cognition and affect in general have been observed in humans (Halpern, 2000), as well as animals (Beatty, 1979), and structural and biochemical sex differences have also been demonstrated (Arnold and Gorski, 1984). Furthermore, a study on residual cannabinoid effects in humans showed that males exhibited poorer performance on tests of cognition relative to females (Pope and Yurgelun-Todd, 1996), whereas a more recent human study found that daily cannabis use was associated with a five-fold increase in anxiety and depression in young females (Patton *et al.*, 2002). Some animal studies have shown that male rats are more sensitive to many of the behavioural effects of cannabinoids (Fernández-Ruiz *et al.*, 1992; Navarro *et al.*, 1996). Further studies should compare the results obtained in the present study using female rats with those found with male rats.

The research available to date on early versus late cannabis exposure is far from conclusive. Most studies have largely focused on the acute, and chronic effects of cannabinoids, rather than residual changes. Of increasing concern is the putative link between the time at first initiation of cannabis and lasting neurobehavioural alterations. With the onset of cannabis use occurring earlier amongst humans, there is an important need to confirm whether early life cannabis initiation has deleterious effects on psychological and social development.

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