

Appendix 1 to Isingrini E, Perret L, Rainer Q, et al. Selective genetic disruption of the dopaminergic, serotonergic and noradrenergic neurotransmission systems: insights on motor, emotional and addictive behaviour. *J Psychiatry Neurosci* 2015.

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Supplemental Information

Figure S1 : Motor functions.

Figure S2 : Acute locomotor response to cocaine according to time.

Figure S3 : Acute locomotor response to amphetamine according to time.

Table S1: Breeding strategy

Table S2 : Detailed statistical analysis

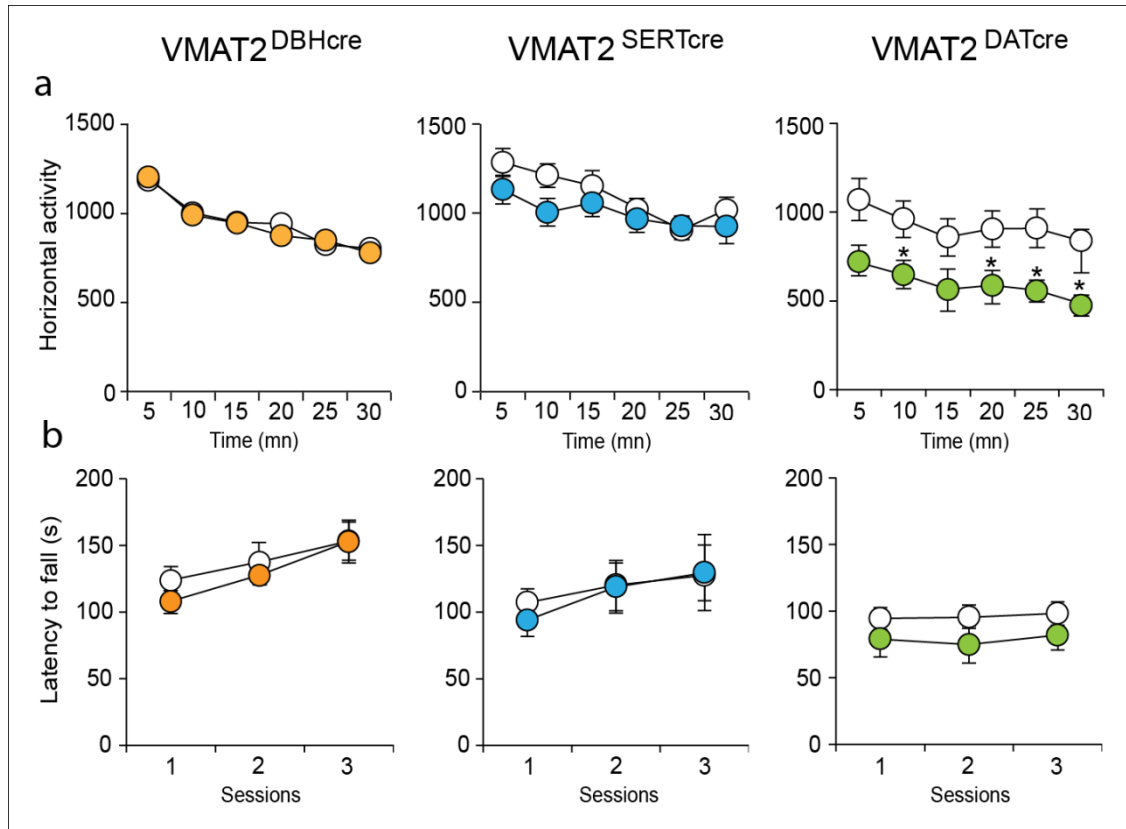


Figure S1 : Motor functions.

(a) Spontaneous locomotion over 30 minutes is decreased in the VMAT2^{DATcre}-HET mice (right) compared to their WT littermates while a similar locomotor pattern between HET and WT is observed in the VMAT2^{DBHcre} (left) and VMAT2^{SERTcre} lines (middle). *p<0.05 indicates a significant difference between WT and HET. (b) Motor coordination assessed during 3 consecutive sessions in a rotarod is unaltered in HET mice compared to their respective WT in the 3 mice lines.

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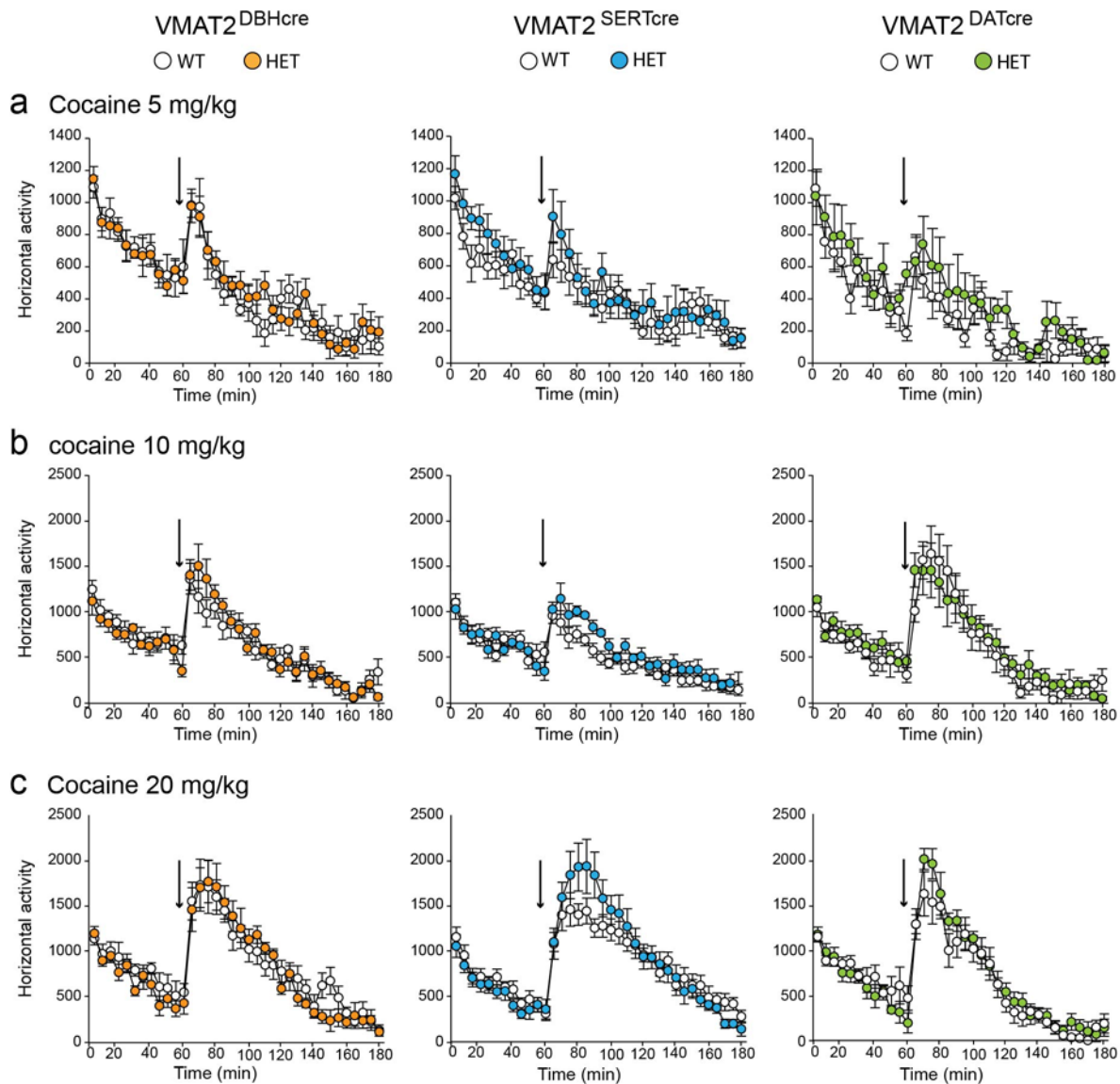


Figure S2 : Acute locomotor response to cocaine according to time.

Acute 2-hrs locomotor response to cocaine at concentration of (a) 5 mg/kg, (b) 10 mg/kg and (c) 20 mg/kg, after 1-hr habituation in WT and HET mice of the $VMAT2^{DBHcre}$ (left), $VMAT2^{SERTcre}$ (middle) and $VMAT2^{DATcre}$ (right). The black arrow indicate the time of i.p. cocaine injection.

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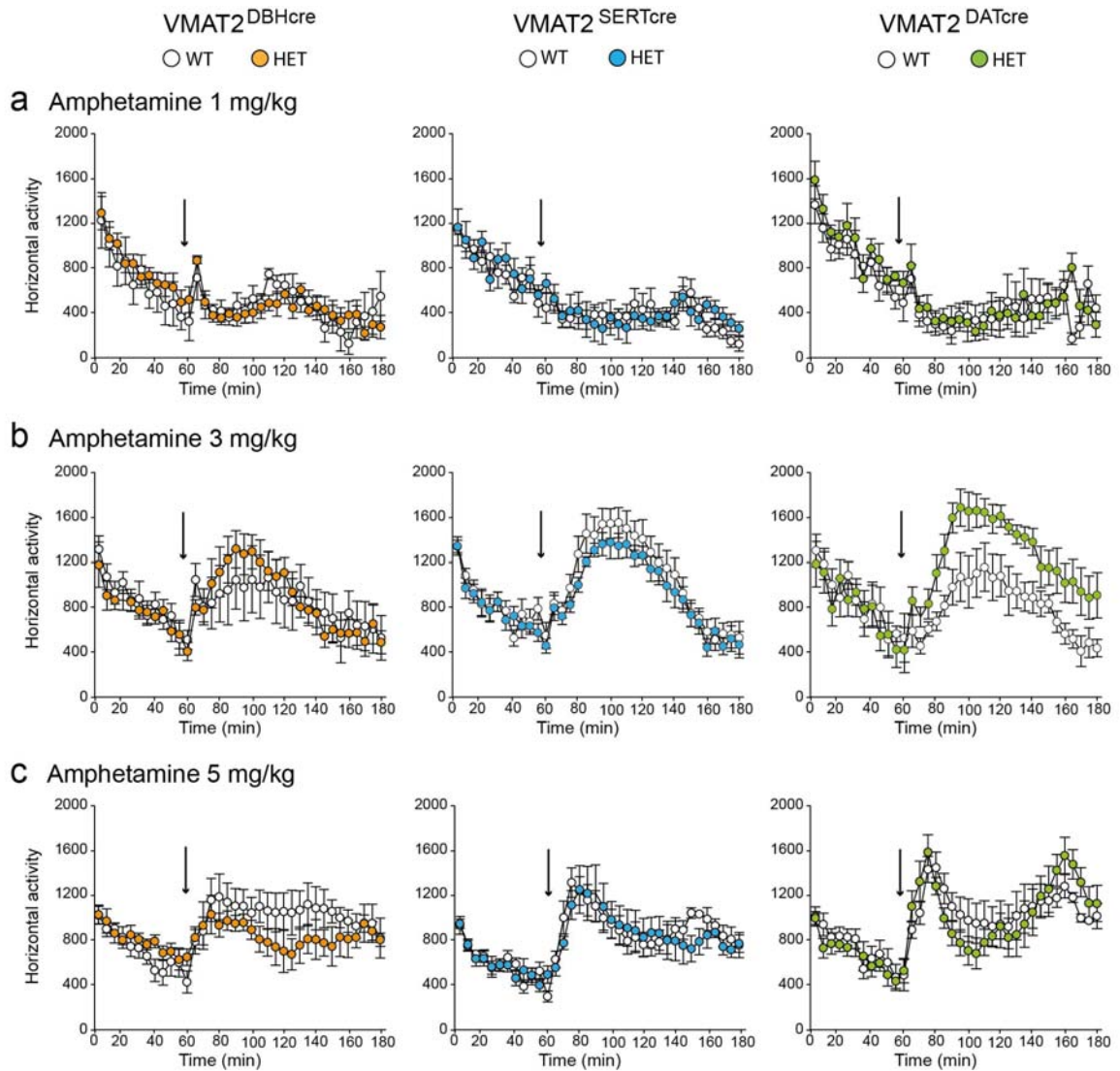


Figure S3 : Acute locomotor response to amphetamine according to time.

Acute 2-hrs locomotor response to amphetamine at concentration of (a) 1 mg/kg, (b) 3 mg/kg and (c) 5 mg/kg, after 1-hr habituation in WT and HET mice of the $VMAT2^{DBHcre}$ (left), $VMAT2^{SERTcre}$ (middle) and $VMAT2^{DATcre}$ (right). The black arrow indicate the time of i.p. amphetamine injection.

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Table S1: Breeding strategy

The heterozygote VMAT2 floxed mice crossed with heterozygote DBHcre, SERTcre and DATcre mice allowed obtaining double heterozygote mice which were crossed between them to generate: 3 genotypes WT, HET, KO.

	VMAT2 ^{DBHcre}	VMAT2 ^{SERTcre}	VMAT2 ^{DATcre}
WT	VMAT2 ^{+/+} DBH ^{cre/+}	VMAT2 ^{+/+} SERT ^{cre/+}	VMAT2 ^{+/+} DAT ^{cre/+}
HET	VMAT2 ^{lox/+} DBH ^{cre/+}	VMAT2 ^{lox/+} SERT ^{cre/+}	VMAT2 ^{lox/+} DAT ^{cre/+}
KO	VMAT2 ^{lox/lox} DBH ^{cre/+}	VMAT2 ^{lox/lox} SERT ^{cre/+}	VMAT2 ^{lox/lox} DAT ^{cre/+}

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Table S2 : Detailed statistical analysis (WT : Wild-type; HET : Heterozygote; KO : Knock-out; VMAT2 : Vesicular monoamine transporter 2; DBH : Dopamine β -hydroxylase; SERT : Serotonin transporter; DAT : Dopamine transporter; HPLC : High performance liquide chromatography; NE : Norepinephrine; 5HT : Serotonin; DA : Dopamine; EPM : Elevated plus maze; FST : Forced swim test; NSF : Novelty suppressed feeding test; CPP : Conditioned place preference).

Figure	test	Parameter	Numbers	Statistical test	Significance	Post-hoc test (group effect)
1c left	HPLC	Whole brain tissu content ($\mu\text{g/g}$)	VMAT2 ^{DBHcre} WT n=5 HET n=5 KO n=6	Kruskal-Wallis ANOVA	DA : H (2, 16) =1,135125 p =,5669	WT vs KO : U=0 p=,006 (<,033)* HET vs KO : U=0 p=,006 (<,033)* WT vs HET : U=15 p=,75
					5HT : H (2, 16) =,0397059 p =,9803	
1c middle	HPLC	Whole brain tissu content ($\mu\text{g/g}$)	VMAT2 ^{SERTcre} WT n=5 HET n=5 KO n=5	Kruskal-Wallis ANOVA	NE : H (2, 16) =10,62794 p =,0049	WT vs KO : U=0 p=,009 (<,033)* HET vs KO : U=0 p=,009 (<,033)* WT vs HET : U=12 p=,92
					DOPAC : H (2, 16) =,4044118 p =,8169	
1c right	HPLC	Whole brain tissu content ($\mu\text{g/g}$)	VMAT2 ^{DATcre} WT n=8 HET n=5 KO n=3	Kruskal-Wallis ANOVA	HVA : H (2, 16) =,2647059 p =,8760	WT vs KO : U=0 p=,014 (<,033)* HET vs KO : U=0 p=,025 (<,033)* WT vs HET : U=15 p=,46
					HIAA : H (2, 16) =,5941176 p =,7430	
1d left	HPLC	Ratio	VMAT2 ^{DBHcre} WT n=5 HET n=5 KO n=6	Kruskal-Wallis ANOVA	DA : H (2, 16) =7,240809 p =,0268	WT vs KO : U=0 p=,006 (<,033)* HET vs KO : U=0 p=,006 (<,033)* WT vs HET : U=10 p=,60
					5HT : H (2, 16) =1,763531 p =,4141	
1d middle	HPLC	Ratio	VMAT2 ^{SERTcre} WT n=5	Kruskal-Wallis ANOVA	NE : H (2, 16) =2,057353 p =,3575	WT vs KO : U=0 p=,006 (<,033)* HET vs KO : U=0 p=,006 (<,033)* WT vs HET : U=10 p=,60
					DOPAC : H (2, 16) =,2220588 p =,8949	
					HVA : H (2, 16) =,1632353 p =,9216	
					HIAA : H (2, 16) =,6455882 p =,7241	
					DOPAC/DA : H (2, 16) =2,451471 p =,2935	
					HVA/DA : H (2, 16) =,9338235 p =,6269	
					DOPAC/NE : H (2, 16) =10,69853 p =,0048	
					HIAA/5HT : H (2, 16) =1,392647 p =,4984	
					DOPAC/DA : H (2, 15) =0,000000 p =1,000	
					HVA/DA : H (2, 15) =4,580000 p =,1013	

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			HET n=5 KO n=5		DOPAC/NE : H (2, 15) =2,060000 p =,3570 HIAA/5HT : H (2, 15) =9,980000 p =,0068	WT vs KO : U=0 p=,009 (<,033)* HET vs KO : U=0 p=,009 (<,033)* WT vs HET : U=7 p=,25
1d right	HPLC	Ratio	VMAT2 ^{DATcre} WT n=8 HET n=5 KO n=3	Kruskal-Wallis ANOVA	DOPAC/DA : H (2, 16) =6,896691 p =,0318 HVA/DA : H (2, 16) =7,240809 p =,0268 DOPAC/NE : H (2, 16) =1,682353 p =,4312 HIAA/5HT : H (2, 16) =5,470588 p =,0649	WT vs KO : U=0 p=,014 (<,033)* HET vs KO : U=0 p=,025 (<,033)* WT vs HET : U=19 P=,88 WT vs KO : U=0 p=,014 (<,033)* HET vs KO : U=0 p=,025 (<,033)* WT vs HET : U=15 p=,46
2a left	HPLC	NE concentration (µg/g)	VMAT2 ^{DBHcre} WT n=3 HET n=4	Mann-Whitney U Test	LC : U=0 p=,034 (<,05)*	
2a middle	HPLC	5HT concentration (µg/g)	VMAT2 ^{SERTcre} WT n=4 HET n=6	Mann-Whitney U Test	Raphe : U=3 p=,05 (<,05) *	
2a right	HPLC	DA concentration (µg/g)	VMAT2 ^{DATcre} WT n=9 HET n=11(VTA) / 10(SN)	Mann-Whitney U Test	VTA : U=24 p=,05 (<,05)* SN : U=10 p=,004 (<,05)**	
3a left	EPM	Time (%)	VMAT2 ^{DBHcre} WT n=19 HET n=20	Mann-Whitney U Test	Open arms : U=172,5 p=,62 Closed arms : U=172 p=,67	
3a middle	EPM	Time (%)	VMAT2 ^{SERTcre} WT n=14 HET n=12	Mann-Whitney U Test	Open arms : U=61 p=,24 Closed arms : U=60,5 p=,23	
3a right	EPM	Time (%)	VMAT2 ^{DATcre} WT n=9 HET n=9	Mann-Whitney U Test	Open arms : U=32,5 p=,48 Closed arms : U=33 p=,51	
3b left	NSF	Eating latency (s)	VMAT2 ^{DBHcre} WT n=10 HET n=10	Mann-Whitney U Test	U=43 p=,60	
3b middle	NSF	Eating latency (s)	VMAT2 ^{SERTcre} WT n=8	Mann-Whitney U Test	U=23,5 p=,95	

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			HET n=6			
3b right	NSF	Eating latency (s)	VMAT2 ^{DA1cre} WT n=8 HET n=8	Mann-Whitney U Test		U=26,5 p=,56
3c left	FST	Immobility (%)	VMAT2 ^{DBHcre} WT n=16 HET n=16	Mann-Whitney U Test		U=124 p=,88
3c middle	FST	Immobility (%)	VMAT2 ^{SERTcre} WT n=8 HET n=7	Mann-Whitney U Test		U=24 p=,64
3c right	FST	Immobility (%)	VMAT2 ^{DA1cre} WT n=9 HET n=9	Mann-Whitney U Test		U=25,5 p=,18
3d left	Sucrose preference test	Sucrose preference (%)	VMAT2 ^{DBHcre} WT n=10 HET n=9	Mann-Whitney U Test		U=40 p=,68
3d middle	Sucrose preference test	Sucrose preference (%)	VMAT2 ^{SERTcre} WT n=10 HET n=8	Mann-Whitney U Test		U=39 p=,93
3d right	Sucrose preference test	Sucrose preference (%)	VMAT2 ^{DA1cre} WT n=10 HET n=10	Mann-Whitney U Test		U=39 p=,41
4a left	Acute locomotor response to cocaine	30-min horizontal activity	VMAT2 ^{DBHcre} WT n=6, 6, 6 HET n=6, 6, 6	Kruskal-Wallis ANOVA	H (5, 36) =21,19820 p =,0007	5 mg/kg : U=16 p=,75 10 mg/kg : U=12 p=,34 20 mg/kg : U=13 p=,42
4a middle	Acute locomotor response to cocaine	30-min horizontal activity	VMAT2 ^{SERTcre} WT n=7, 10, 10 HET n=8, 7, 9	Kruskal-Wallis ANOVA	H (5, 51) =30,97827 p =,0000	5 mg/kg : U=23 p=,56 10 mg/kg : U=12 p=,024 (<,033)* 20 mg/kg : U=31 p=,25
4a right	Acute locomotor response to cocaine	30-min horizontal activity	VMAT2 ^{DA1cre} WT n=5, 6, 6 HET n=6, 6, 6	Kruskal-Wallis ANOVA	H (5, 35) =19,68698 p =,0014	5 mg/kg : U=16 p=,75 10 mg/kg : U=12 p=,34 20 mg/kg : U=13 p=,42
4b left	Cocaine sensitization (20 mg/kg)	30-min horizontal activity	VMAT2 ^{DBHcre} WT n=10	Wilcoxon Matched Pairs Test	Day 1 vs Day 8 : WT : T=0 p=,005 (<,01)**	

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			HET n=10		HET : T=8 p=,047 (<,05)*	
4b middle	Cocaine sensitization (20 mg/kg)	30-min horizontal activity	VMAT2 ^{SERTcre} WT n=9 HET n=8	Wilcoxon Matched Pairs Test	Day 1 vs Day 8 : WT : T=0 p=,008 (<,01)** HET : T=11 p=,33	
4b right	Cocaine sensitization (20 mg/kg)	30-min horizontal activity	VMAT2 ^{DATcre} WT n=8 HET n=8	Wilcoxon Matched Pairs Test	Day 1 vs Day 8 : WT : T=0 p=,012 (<,05)* HET : T=1 p=,017 (<,05)*	
4c left	Acute locomotor response to amphetamine	2-hrs horizontal activity	VMAT2 ^{DBHcre} WT n=5, 6, 6 HET n=7, 7, 6	Kruskal-Wallis ANOVA	H (5, 37) =19,02934 p =,0019	1 mg/kg : U=14 p=,57 3 mg/kg : U=19 p=,77 5 mg/kg : U=11 p=,26
4c middle	Acute locomotor response to amphetamine	2-hrs horizontal activity	VMAT2 ^{SERTcre} WT n=6,7,6 HET n=6,7,6	Kruskal-Wallis ANOVA	H (5, 38) =25,03355 p =,0001	1 mg/kg : U=17 p=,87 3 mg/kg : U=17 p=,34 5 mg/kg : U=16 p=,75
4c right	Acute locomotor response to amphetamine	2-hrs horizontal activity	VMAT2 ^{DATcre} WT n=5, 10, 6 HET n=5, 10, 6	Kruskal-Wallis ANOVA	H (5, 42) =28,63477 p =,0000	1 mg/kg : U=12 p=,92 3 mg/kg : U=13 p=,005 (<,033)* 5 mg/kg : U=18 p=1
4d left	CPP	Conditioned preference for drug-paired place (%)	VMAT2 ^{DBHcre} WT n=5, 6, 6 HET n=7, 7, 6	Kruskal-Wallis ANOVA	H (5, 41) =20,27383 p =,0011	0 mg/kg : U=21 p=1 1 mg/kg : U=21 p=,42 3 mg/kg : U=19 p=,89
4d middle	CPP	Conditioned preference for drug-paired place (%)	VMAT2 ^{SERTcre} WT n=5, 8, 8 HET n=6, 8, 8	Kruskal-Wallis ANOVA	H (5, 43) =23,49545 p =,0003	0 mg/kg : U=13 p=,71 1 mg/kg : U=30 p=,83 3 mg/kg : U=31 p=,92
4d right	CPP	Conditioned preference for drug-paired place (%)	VMAT2 ^{DATcre} WT n=5, 5, 5 HET n=5, 6, 7	Kruskal-Wallis ANOVA	H (5, 32) =23,13563 p =,0003	0 mg/kg : U=11 p=,75 1 mg/kg : U=16 p=,81 3 mg/kg : U=8 p=,39
S1 left	Spontaneous locomotion	30-min horizontal activity	VMAT2 ^{DBHcre} WT n=40 HET n=45	Mann-Whitney U Test	5 min : U=866 p=,76 10 min : U=884 p=,89 15 min : U=900 p=1 20 min : U=745 p=,17 25 min : U=829,5 p=,53 30 min : U=844 p=,62	
S1 middle	Spontaneous locomotion	30-min horizontal activity	VMAT2 ^{SERTcre} WT n=8 HET n=8	Mann-Whitney U Test	5 min : U=19 p=,17 10 min : U=14 p=,06 15 min : U=24 p=,40	

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					20 min : U=25 p=,46 25 min : U=32 p=1 30 min : U=30 p=,83
S1 right	Spontaneous locomotion	30-min horizontal activity	VMAT2 ^{DATcre} WT n=8 HET n=9	Mann-Whitney U Test	5 min : U=17 p=,067 10 min : U=14 p=,034 (<,05)* 15 min : U=20 p=,12 20 min : U=15 p=,043 (<,05)* 25 min : U=12 p=,021 (<,05)* 30 min : U=13 p=,027 (<,05)*