**Supplementary Information**

**Supplementary Figures and Tables**

|  |  |  |
| --- | --- | --- |
| **Behaviour** | **Two-way ANOVA**  **Inactive lever presses** | **Two-way ANOVA**  **Wasted lever presses** |
| **Acquisition**  **Cocaine SA (0,2 mg/kg)** | **Session: F12,360=1.19, p=0.28, NS**  **Genotype: F2, 30= 0.17, p=0.84, NS**  **Interaction: F24, 360 = 0.83, p=0.7, NS** | **F12,360=1.08, p=0.38, NS**  **F2, 30= 0.1, p=0.9, NS**  **F24, 360 = 0.63, p=0.91, NS** |
| **Dose-response (0,1-0,8 mg/kg) cocaine SA** | **Cocaine dose: F3,75=7.1, p=0.0003**  **Genotype: F2, 25= 0.18, p=0.83, NS**  **Interaction: F6, 75 = 1.22, p=0.3, NS** | **F3,75=9.22, p<0.0001**  **F2, 25= 0.81, p=0.45, NS**  **F6, 75 = 0.78, p=0.58, NS** |
| **Progressive Ratio (0,2-0,4 mg/kg) cocaine SA** | **Cocaine dose: F1,23=15.08, p=0.0008**  **Genotype: F2, 23= 0.37, p=0.69, NS**  **Interaction: F2, 23 = 0.23, p=0.8, NS** | **F1,23=3.36, p=0.08, NS**  **F2, 23= 3.23, p=0.058, NS**  **F2, 23 = 2.85, p=0.078, NS** |
| **Cue-induced reinstatement** | **Reinstatement: F1,23=4.23, p=0.051, NS**  **Genotype: F2, 23= 0.46, p=0.64, NS**  **Interaction: F2, 23 = 0.58, p=0.57, NS** |  |
| **Stress-induced reinstatement** | **Reinstatement: F1,23=7.62, p=0.011**  **Genotype: F2, 23= 0.12, p=0.88, NS**  **Interaction: F2, 23 = 0.03, p=0.97, NS** |  |
| **Cocaine (10 mg/kg)-induced reinstatement** | **Reinstatement: F1,23=0.05, p=0.82, NS**  **Genotype: F2, 23= 0.29, p=0.74, NS**  **Interaction: F2, 23 = 1.36, p=0.28, NS** |  |

**Table S1: Statistics on inactive lever and perseverative responding (wasted lever presses during the time-out period) during cocaine self-administration (SA) of WT, α5SNP and α5KO rats.**

Two-way ANOVAs performed on inactive or wasted lever presses during the different phases of the cocaine SA study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Behaviour** | **WT** | **α5SNP** | **α5KO** | **One-way ANOVA** |
| **Acquisition**  **FR-1** | **2.45**  +/- 0.15 | **2.5**  +/- 0.17 | **2.58**  +/- 0.15 | F (2, 30) = 0.18  P = 0.83, NS |
| **Acquisition**  **FR-2** | **2**  +/- 0 | **2**  +/- 0 | **2**  +/- 0 | Not Applicable  (SEMs=0) |
| **Acquisition**  **FR-3** | **2.27**  +/- 0.14 | **2.2**  +/- 0.13 | **2.33**  +/- 0.14 | F (2, 30) = 0.23  P = 0.8, NS |
| **Acquisition**  **FR-4** | **2**  +/- 0 | **2**  +/- 0 | **2**  +/- 0 | Not Applicable  (SEMs=0) |
| **Acquisition**  **FR-5** | **2.36**  +/- 0.15 | **2.6**  +/- 0.16 | **2.67**  +/- 0.14 | F (2, 30) = 1.12  P = 0.34, NS |
| **Extinction** | **6.77**  +/- 0.6 | **5**  +/- 0.5 | **6.1**  +/- 0.45 | F (2, 23) = 2.86  P = 0.0776, NS |

**Table S2: Number of sessions to reach the criterion during cocaine self-administration (SA) of WT, α5SNP and α5KO rats.**

The one-way ANOVAs were performed on the number of sessions to reach the criterion during the different phases of the cocaine SA study.

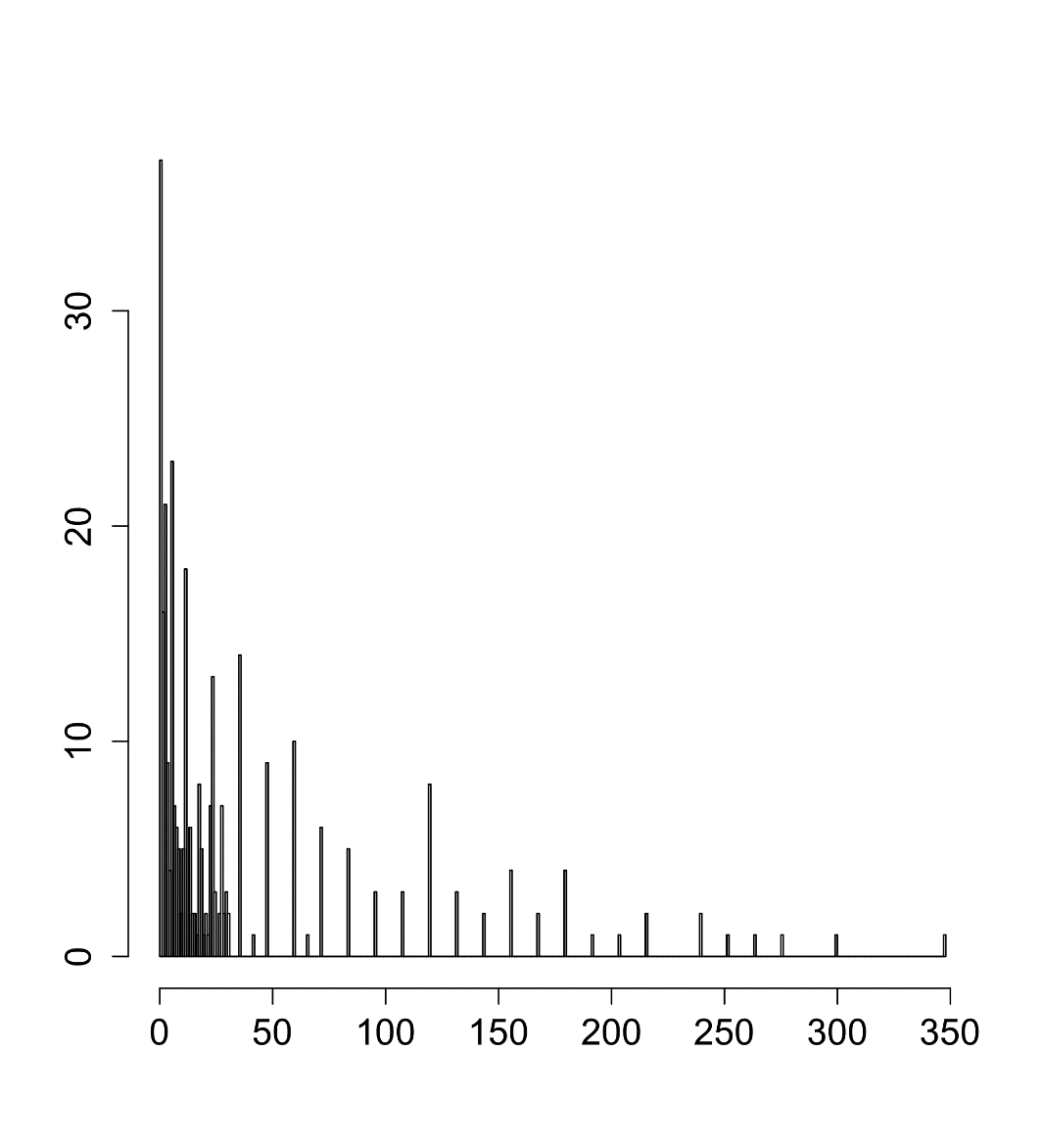
|  |  |  |
| --- | --- | --- |
|  | | **Mean (SD) or N (%)** |
| Age | | 39 (9) |
| Gender | *Men* | 234 (76%) |
| *Women* | 72 (24%) |
| Homelessness ≥3 months | | 89 (29%) |
| At least one lifetime SA | | 115 (38%) |
| Number of cigarettes smoked / day | | 18 (11) |
| 3 comorbid lifetime SUDs or more (except tobacco) | | 257 (44%) |
| Lifetime SUD diagnoses | *Opiates* | 129 (42%) |
| *Alcohol* | 224 (75%) |
| *Cannabis* | 243 (81%) |
| *Sedatives* | 170 (56%) |
| Age at onset of cocaine use (years) | | 23 (6) |
| Weekly cocaine use during self-reported worst period of CUD (daily *vs.* non-daily) | | 191 (62%) |
| Number of DSM-IV criteria for CUD | | 4.9 (1.8) |
| Delay to relapse from CUD after cessation (months): *Mean (SD)*  *Median (IQR)* | | 37 (58)  13 (4-36) |

**Table S3: description of the clinical sample with data about CUD relapse after removal of outliers, N =306.** SD, standard deviation;SUD, substance use disorder; CUD, cocaine use disorder; IQR, interquartile range.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***SNP ID*** | ***Position on chr15 (bp)*** | ***alleles*** | ***MAF in the European superpopulation*** | ***distance from rs950776 (bp)*** | ***LD*** | | ***NES*** | ***NES x R2*** |
| D' | R2 |
| rs950776 | 78926018 | (T/C) | 0.325 | 0 | 1 | 1 | 0.63 | 0.63 |
| rs8023462 | 78914734 | (C/T) | 0.336 | -11284 | 0.9816 | 0.917 | -0.64 | -0.58688 |
| rs2904130 | 78916622 | (C/G) | 0.335 | -9396 | 0.977 | 0.9126 | -0.64 | -0.584064 |
| rs4887070 | 78916187 | (C/T) | 0.338 | -9831 | 0.9815 | 0.9088 | -0.63 | -0.572544 |
| rs62010332 | 78918762 | (G/C) | 0.325 | -7256 | 0.9275 | 0.8603 | 0.63 | 0.541989 |
| rs1948 | 78917399 | (A/G) | 0.3191 | -8619 | 0.9262 | 0.8346 | -0.65 | -0.54249 |
| rs7178270 | 78921077 | (C/G) | 0.3638 | -4941 | 0.9904 | 0.826 | 0.69 | 0.56994 |
| rs62010327 | 78892784 | (G/A) | 0.34 | -33234 | 0.9212 | 0.7935 | 0.68 | 0.53958 |
| rs7495518 | 78900574 | (C/T) | 0.333 | -25444 | 0.89 | 0.764 | 0.67 | 0.51188 |
| rs62010328 | 78894971 | (C/T) | 0.333 | -31047 | 0.89 | 0.764 | 0.66 | 0.50424 |
| rs2869546 | 78907345 | (C/T) | 0.3499 | -18673 | 0.92 | 0.7574 | -0.69 | -0.522606 |
| rs2067808 | 78911780 | (G/A) | 0.3509 | -14238 | 0.9199 | 0.7539 | 0.66 | 0.497574 |
| rs3743075 | 78909452 | (T/C) | 0.341 | -16566 | 0.8886 | 0.7351 | -0.7 | -0.51457 |
| rs79609284 | 78928411 | (G/A) | 0.336 | 2393 | 0.8757 | 0.7298 | 0.63 | 0.459774 |
| rs3743074 | 78909480 | (G/A) | 0.3429 | -16538 | 0.8883 | 0.7281 | -0.69 | -0.502389 |
| rs111725959 | 78899346 | (G/A) | 0.3429 | -26672 | 0.8883 | 0.7281 | 0.67 | 0.487827 |
| rs7182583 | 78899210 | (G/C) | 0.3429 | -26808 | 0.8883 | 0.7281 | 0.67 | 0.487827 |
| rs514743 | 78884227 | (T/A) | 0.3429 | -41791 | 0.8883 | 0.7281 | -0.68 | -0.495108 |
| rs17408276 | 78881618 | (T/C) | 0.3429 | -44400 | 0.8883 | 0.7281 | 0.67 | 0.487827 |
| rs3743073 | 78909539 | (G/T) | 0.3439 | -16479 | 0.8881 | 0.7246 | -0.69 | -0.499974 |
| rs472054 | 78887994 | (A/G) | 0.3439 | -38024 | 0.8881 | 0.7246 | -0.67 | -0.485482 |
| rs660652 | 78887832 | (A/G) | 0.3439 | -38186 | 0.8881 | 0.7246 | -0.67 | -0.485482 |
| rs615470 | 78885988 | (T/C) | 0.3439 | -40030 | 0.8881 | 0.7246 | -0.67 | -0.485482 |
| rs584135 | 78883628 | (A/G) | 0.3439 | -42390 | 0.8881 | 0.7246 | -0.68 | -0.492728 |
| rs692780 | 78876505 | (C/G) | 0.3419 | -49513 | 0.8745 | 0.7088 | -0.69 | -0.489072 |
| rs61012457 | 78865694 | (C/G) | 0.3419 | -60324 | 0.8745 | 0.7088 | 0.68 | 0.481984 |
| rs57945453 | 78862845 | (C/T) | 0.3419 | -63173 | 0.8745 | 0.7088 | 0.72 | 0.510336 |
| rs11637635 | 78877150 | (A/G) | 0.3429 | -48868 | 0.8743 | 0.7054 | -0.69 | -0.486726 |
| rs471889 | 78870235 | (T/C) | 0.3449 | -55783 | 0.874 | 0.6986 | -0.65 | -0.45409 |
| rs495090 | 78870003 | (A/G) | 0.3449 | -56015 | 0.874 | 0.6986 | -0.66 | -0.461076 |
| rs495956 | 78869930 | (C/T) | 0.3449 | -56088 | 0.874 | 0.6986 | -0.66 | -0.461076 |
| rs1878399 | 78912003 | (G/C) | 0.3907 | -14015 | 0.9498 | 0.6777 | -0.71 | -0.481167 |
| rs4352017 | 78912204 | (A/C) | 0.3936 | -13814 | 0.9546 | 0.676 | -0.69 | -0.46644 |
| rs8025188 | 78912278 | (C/G) | 0.3926 | -13740 | 0.9496 | 0.6718 | -0.69 | -0.463542 |
| rs57728226 | 78929350 | (G/C) | 0.3728 | 3332 | 0.9025 | 0.66 | 0.75 | 0.495 |
| rs36045869 | 78929498 | (C/T) | 0.3738 | 3480 | 0.9023 | 0.657 | 0.75 | 0.49275 |
| rs3743077 | 78894896 | (C/T) | 0.3867 | -31122 | 0.9252 | 0.6539 | 0.71 | 0.464269 |
| rs12901300 | 78892952 | (G/A) | 0.3867 | -33066 | 0.9252 | 0.6539 | 0.7 | 0.45773 |
| rs12911602 | 78891449 | (T/C) | 0.3867 | -34569 | 0.9252 | 0.6539 | 0.7 | 0.45773 |
| rs6495307 | 78890321 | (C/T) | 0.3867 | -35697 | 0.9252 | 0.6539 | 0.7 | 0.45773 |
| rs56276142 | 78889795 | (T/C) | 0.3867 | -36223 | 0.9252 | 0.6539 | 0.71 | 0.464269 |
| rs647041 | 78880481 | (T/C) | 0.3867 | -45537 | 0.9252 | 0.6539 | -0.73 | -0.477347 |
| rs77403874 | 78903165 | (T/C) | 0.3887 | -22853 | 0.925 | 0.6481 | 0.68 | 0.440708 |
| rs183822442 | 78902775 | (A/G) | 0.3887 | -23243 | 0.925 | 0.6481 | 0.68 | 0.440708 |
| rs139978901 | 78902026 | (C/A) | 0.3887 | -23992 | 0.925 | 0.6481 | 0.68 | 0.440708 |
| rs6495306 | 78865893 | (G/A) | 0.3877 | -60125 | 0.9201 | 0.644 | -0.76 | -0.48944 |
| rs588765 | 78865425 | (T/C) | 0.3877 | -60593 | 0.9201 | 0.644 | -0.76 | -0.48944 |
| rs555018 | 78879242 | (G/A) | 0.3867 | -46776 | 0.9152 | 0.6399 | -0.76 | -0.486324 |
| rs871058 | 78858491 | (G/A) | 0.3131 | -67527 | 0.8213 | 0.6384 | 0.71 | 0.453264 |
| rs621849 | 78872861 | (G/A) | 0.3897 | -53157 | 0.9198 | 0.6382 | -0.7 | -0.44674 |
| rs10709956 | 78872834 | (A/-) | 0.3897 | -53184 | 0.9198 | 0.6382 | -0.7 | -0.44674 |
| rs680244 | 78871288 | (T/C) | 0.3897 | -54730 | 0.9198 | 0.6382 | -0.73 | -0.465886 |
| rs601079 | 78869579 | (T/A) | 0.3897 | -56439 | 0.9198 | 0.6382 | -0.7 | -0.44674 |
| rs8040544 | 78904261 | (G/A) | 0.3857 | -21757 | 0.9104 | 0.6358 | 0.68 | 0.432344 |
| rs481134 | 78877563 | (A/G) | 0.3857 | -48455 | 0.9104 | 0.6358 | -0.73 | -0.464134 |
| rs3829787 | 78856266 | (C/T) | 0.328 | -69752 | 0.7952 | 0.6238 | 0.75 | 0.46785 |
| rs11637890 | 78935419 | (C/G) | 0.3678 | 9401 | 0.8646 | 0.6188 | 0.75 | 0.4641 |
| rs11633223 | 78935476 | (T/C) | 0.3678 | 9458 | 0.8646 | 0.6188 | 0.75 | 0.4641 |
| rs7173512 | 78849914 | (C/T) | 0.33 | -76104 | 0.7946 | 0.6173 | -0.74 | -0.456802 |
| rs4275821 | 78849541 | (C/T) | 0.33 | -76477 | 0.7946 | 0.6173 | -0.73 | -0.450629 |
| rs4366683 | 78912203 | (C/T) | 0.4205 | -13815 | 0.9525 | 0.6022 | -0.69 | -0.415518 |

**Table S4: Characteristics of SNPs in high linkage disequilibrium with rs950776 and their normalized effect size (NES) according to *GTEx portal.***

**Table S5: significant eQTLs for the six SNPs tested with relapse of cocaine use disorder. File available at** <https://www.editorialmanager.com/proneu/download.aspx?id=22319&guid=81833ff4-1cb6-4f46-b152-0f1e0a992627&scheme=1>

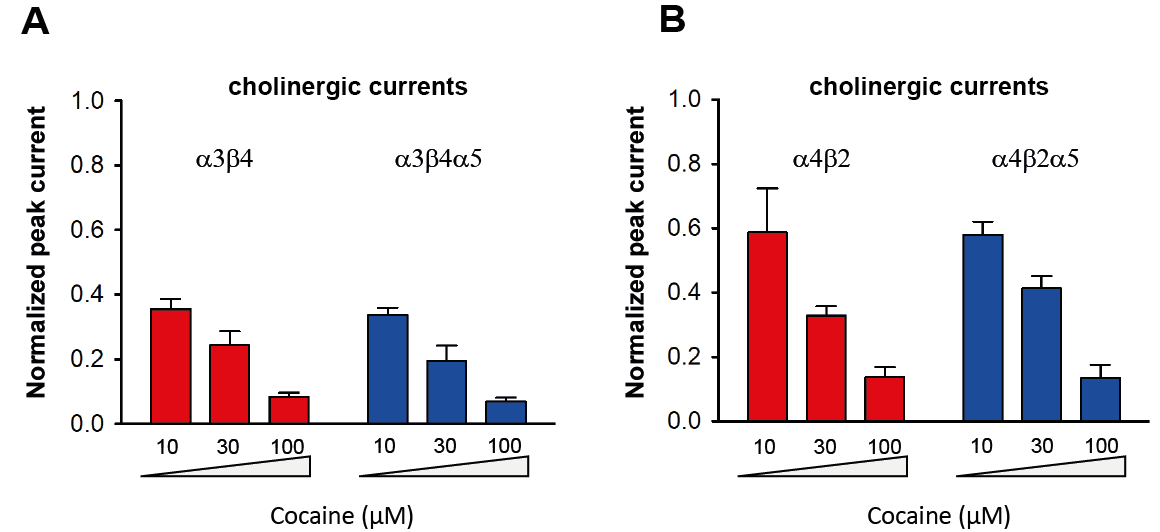
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**Number of patients**

**Months from cessation of cocaine use to relapse**

**Fig. S1: Distribution of the delay to relapse to cocaine use (months) in the human sample**

**Fig. S2: Linkage disequilibrium in 21 SNPs from the *CHRNA5-A3-B4* cluster according to *HAPLOVIEW***



**Fig. S3: (A) Absence of effect of the presence of the α5 subunit on cocaine-induced inhibition of cholinergic current on α3β4-containing nicotinic receptors in oocytes.** Normalized peak current = Ipeak(ACh+cocaine)/Ipeak(ACh). Ach concentration: 30µM.

The two-way ANOVA performed on normalized peak current indicated a significant effect of cocaine concentration(F2,8=40.02, p<0.0001; partial η2=0.91); but not of α5-subunit addition (F1,4=3.16, p=0.15, NS; partial η2=0.35) and no interaction (F1,4=2.37, p=0.16, NS; partial η2=0.37).

**(B) Absence of effect of the presence of the α5 subunit on cocaine-induced inhibition of cholinergic current on α4β2-containing nicotinic receptors in oocytes.**

Normalized peak current = Ipeak(ACh+cocaine)/Ipeak(ACh). Ach concentration: 30µM.

The two-way ANOVA performed on normalized peak current indicated a significant effect of cocaine concentration(F2,8=39.03, p<0.0001; partial η2=0.9); but not of α5-subunit addition (F1,4=0.12, p=0.75, NS; partial η2=0.04) and no interaction (F1,4=0.51, p=0.62, NS; partial η2=0.11).

Mean and SEM are represented.