## Title:

# Environment-dependent behavioral traits and experiential factors shape addiction vulnerability

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## Abstract:

The transition from controlled drug use to drug addiction depends on an interaction between a vulnerable individual, their environment and a drug. However, the determining factors of this interaction remain elusive. We show in rats that the environment influences the acquisition of drug intake through its effect on behavioral markers of resilience to addiction. In contrast, the development of both compulsive cocaine and alcohol intake is facilitated by the experiential factors associated with the initiation of drug taking in a negative, deprived, state occasioned by the contrast between enriched housing conditions and a relatively impoverished drug-taking setting. Similarly, the acquisition of alcohol drinking as a coping strategy promotes the development of compulsive intake. These data demonstrate that addiction vulnerability lies in environmentally determined experiential factors.

## keywords:

cocaine, alcohol, compulsivity, environmental enrichment, schedule-induced polydipsia

## Short title:

There is more to addiction than a drug

## One Sentence Summary:

Environmental control of the behavioral and experiential factors of vulnerability to acquire, and lose control over, drug use

## Main Text:

Ten to thirty-five percent of individuals recreationally using drugs eventually develop the compulsive drug seeking and taking (*1*) that characterise drug addiction (*2*). It has long been considered that this individual vulnerability to transition from controlled to compulsive drug taking stems from the interaction between a specific genetic background, a vulnerability-inducing environment and the drug (*3*). However, the evident limitations of longitudinal studies in humans, which cannot control environmental and experiential factors (*4, 5*), and the inherent limitations of preclinical animal models (*6*) have made understanding of the nature of these interactions and their underlying mechanisms extremely difficult.

The discovery of inter-individual differences in the vulnerability to develop addiction-like behavior in the rat (*7, 8*), measured by operationalising three key features of the diagnosis of the disorder as defined in the DSM (*9*), has helped to identify factors that mediate the effects of gene x drug interactions on the propensity to engage in drug taking and the vulnerability, or resilience, to addiction (*10*). Thus, high locomotor reactivity to novelty, suggested to operationalize sensation seeking, shown to predict an increased propensity to self-administer stimulants (*11*), has also been shown to be a marker of resilience to the transition to addiction (*7, 12*). This is consistent with evidence that sensation seeking in humans is related to recreational drug use, but not addiction (*13*). Other behavioral traits (*10*), such as anxiety, impulsivity and novelty preference, have instead been shown specifically to predict loss of control over cocaine intake (*14*) or the transition to cocaine addiction in rats (*7, 12*) and in humans (*13*).

It is not yet understood how these behavioral factors of vulnerability are influenced by, or interact with, the environment to shape the propensity to engage in drug taking, nor whether experiential determinants of drug taking, such as enhancement seeking or coping with distress (*4, 15*), are also involved in the vulnerability to compulsively take drugs. The impact of an individual's environment on the vulnerability to addiction has hitherto been considered to be both unidimensional and unidirectional: impoverished environmental conditions such as those faced by low socio-economic groups, or, inferentially, by rodents kept in so-called impoverished housing conditions, are considered to promote addiction (*16*). However, experimental evidence is lacking to support the latter and emerging epidemiological observations bring the former into

question (*17*). Experimentally, rats raised in an enriched environment (EE) seem less likely to self-administer drugs (*18*), yet are more sensitive to the reinforcing effects of drugs than rats raised in standard environment (SE). Thus, EE rats show lower self-administration titration rates than SE rats under fixed ratio schedules of reinforcement (*16, 18*), and have also been reported freely to drink more alcohol in two-bottle choice conditions than SE rats (*19*). These observations are consistent with the epidemiological evidence that individuals from high socio-economic populations suffer premature drug-related deaths (*17*), drink more often and consume higher quantities of alcohol than those from lower socio-economic backgrounds, even though the latter seem to suffer more negative consequences (*20*). It is therefore clear that experiential factors related to drug use, rather than living conditions per se, are important determinants of the vulnerability to addiction across environmental conditions, as also indicated by the sharp rise in drug-related deaths observed in very wealthy individuals (*21, 22*).

We first causally tested the influence of different housing conditions, i.e. EE vs SE (n=24 each) on behavioral traits related to personality factors relevant to addiction, namely anxiety (*14*), sensation seeking (*7, 11, 23*), boredom susceptibility (*12*), reward sensitivity (*24*) and sign-tracking (*25*) (**Fig. S1**), within a multidimensional, pseudo-personality model in the rat **(see supplementary online material)**. EE abolished the drug use proneness/addiction-resilience trait of high locomotor reactivity to novelty (HR), and decreased anxiety-associated behaviors; EE also disrupted the asymmetric approach behavior usually displayed by sign-trackers, in line with previous evidence that EE impairs the attribution of incentive salience to food-paired cues (*26*) (**Fig. 1 and Fig. S2, S3**). EE did not influence each trait independently, but it shaped their relative multidimensional configuration in three distinct pseudo-personality models identified at the population level by cluster analysis (**Fig. 1B**). In particular EE increased the probability of displaying a pseudo-personality driven by sweetness and novelty preference (model 3), as opposed to a pseudo-personality driven by stress reactivity (model 1) preferentially displayed by SE rats (**Fig. 1B**).

We then tested whether the influence of housing conditions on these behavioral traits mediated the well-established effect of EE on the propensity to take drugs. As previously described (*27, 28*), EE decreased the overall propensity of rats to acquire cocaine self-administration (SA) (**Fig. 2A**) as compared to SE. However, the present data revealed that this EE effect was driven by a further decrease in the propensity to acquire cocaine SA in non-vulnerable populations, i.e. rats with a low locomotor response to novelty (low responders, LR), low novelty (LNP) and low saccharine preference (LSP) (**Fig. 2B, 2C** and **Fig. S4-5**).

The increased weight of sweetness and novelty preference to the pseudo-personality shaped by EE, at the expense of locomotor reactivity to novelty, which confers resistance to the transition to addiction (*7, 12*) (**Fig. 2C**), suggests that while decreasing the propensity to self-administer cocaine, EE may promote the switch from controlled to compulsive drug use in vulnerable individuals. We therefore investigated the influence of housing conditions on the individual vulnerability to develop addiction-like behavior following a prolonged period of exposure to cocaine SA (*8, 12, 29*). An other cohort of 48 rats (EE vs SE n=24 each) was exposed to ~50 days of cocaine SA prior to being

tested for their addiction-like behavior, i.e. high motivation for the drug, high persistence of drug taking despite adverse consequences and an inability to refrain from seeking the drug (see (*7, 29*) and **supplementary online material**).

Regardless of their housing conditions, rats were identified as displaying 0, 1, 2 or 3 addiction-like criteria (**Fig. 3A**) **(see supplementary online material)**. As previously described (*7, 29*), the overall population was linearly distributed alongside an addiction severity index (*8*) in which only those rats displaying the three addiction criteria (3-criteria or 3crit) rats, displayed a score that was beyond the standard deviation of the cohort while 0crit, addiction resilient, rats displayed a negative addiction severity score.

The individual vulnerability to develop addiction-like behavior was significantly influenced by housing conditions. Thus, a retrospective analysis revealed that EE rats displayed much higher addiction scores than SE rats (**Fig. 3B**) and that the entire 3crit population was, against expectation, comprised exclusively of EE rats (**Fig. 3C**). The influence of housing conditions on addiction vulnerability was primarily driven by a facilitation of the development of compulsivity and the persistence of drug seeking, and less so by an effect on motivation (**Fig. 3D**), but importantly was not due to overall differences in drug intake (**Fig. 3D**) or to any differential pain sensitivity (*30*) (**Fig. 3D**). This inter-dimensional approach offers unprecedented evidence that EE, while decreasing the propensity to engage in drug use, promotes the development of addiction-like behavior.

We then verified that the facilitatory effect of EE on the development of compulsive drug intake was not specific to cocaine in a self-administration context. In a third experiment, the propensity of rats housed in EE vs SE (n = 12 each) to develop compulsive alcohol intake was assessed after several months of intermittent access to alcohol in a two bottle-choice procedure (*31, 32*). Compared to SE rats, EE rats displayed an increased tendency to relapse to alcohol drinking following several weeks of forced abstinence (**Fig. 4A**) and did so compulsively, in that they specifically persisted in drinking alcohol despite adulteration by quinine (*33*) (**Fig. 4B** and **S6**). Hence, EE rats were eventually seen to be more vulnerable than SE rats to develop two key behavioral features of alcohol use disorder (*2, 34*).

Together, these results demonstrate a bidirectional effect of housing conditions on the propensity to acquire drug SA and the vulnerability to develop compulsive drug taking, a key characteristic of addiction (*2*). While these results seem, at first glance, to be counter-intuitive, they highlight the importance of the experiential factors which here depends on the contrast that exists between rats' living conditions and the drug-taking setting (**Fig. S7**), which has been shown to influence the relative preference between cocaine and heroin (*35*). In contrast to the Rat Park experiment, which did not measure the compulsive nature of drug taking and in which access to the drug was provided in the enriched housing environment itself (*36*), in the present study individuals had access to cocaine or alcohol in a relatively impoverished drug setting. Therefore, EE rats, in marked contrast to SE rats, encountered the drug in a state of relative social, sensory and cognitive deprivation due to the highly salient contrast between their enriched housing conditions and the drug SA context (**Fig. S7**). Such negative environmental contrast likely biases individuals to self-administer drug in the experiential setting, and the drug is taken to ameliorate an internal deficit/distress state

(*5, 37*). In humans, this negative motivational state is frequently associated with the initiation of drug use and to increased vulnerability to addiction (*4, 38*), being moderated or exacerbated by traits influenced by EE in this study, namely sensation seeking, boredom susceptibility/novelty preference and anxiety (*38-40*) .

According to this framework, rather than the housing conditions per se, it is the experiential factors in the drug setting, such as those related to high boredom susceptibility/novelty preference (*12, 41, 42*), that influence the vulnerability to subsequently develop compulsive drug taking. We therefore causally tested the hypothesis that the initial exposure to a drug such as alcohol in a negative experiential setting, and the associated acquisition of alcohol use to cope with distress, promotes the transition to compulsive alcohol intake in rats under similar housing conditions. Thus, in a fourth longitudinal experiment, alcohol was introduced to a cohort of 48 SE rats (*43*) that had been trained to cope with distress in a schedule-induced polydipsia procedure (SIP) (*44, 45*). In this procedure, intermittent food delivery triggers internal distress with which rats learn to cope by developing adjunctive behaviors, such as excessive intake of freely available water (*46*). However not all rats acquire the adjunctive response with water (*47*) (**Fig. 4C**). We therefore hypothesized that only those rats that learn to cope with distress by drinking alcohol and not water would develop compulsive (quinine-resistant) alcohol intake **(see supplementary online material)**.

While some rats learnt to cope with distress triggered by the SIP procedure by drinking water and maintained their established coping strategy after alcohol was introduced in place of water (Water Copers, WC), others only developed that coping strategy with alcohol (Alcohol Copers, AC) (**Fig. 4C**). AC rats, which did not differ from WC rats in terms of total alcohol intake over the course of the 20 days of exposure (**Fig. S8** and **supplementary online material**), specifically developed persistence in drinking alcohol despite adulteration with quinine (**Fig. 4D** and **S8**). This differential vulnerability to develop compulsive alcohol drinking was not due to differences in blood alcohol levels since these were similar in both groups (**Fig. S8**) and was therefore specific to the experiential nature of the SIP context (**Fig. S8**).

Together these results demonstrate that a negative experiential context, may it be internal or triggered by environmental conditions, at the onset of alcohol use is a gateway to the development of compulsive drinking in individuals that had been unable to learn to cope with negative states by alternative means (**Fig. 4D** and **S8**).

Together the present findings provide substantial evidence for the role of environmental and experiential factors in shaping an individual's vulnerability to shift from controlled to compulsive drug taking, which has previously been understood in terms of behavioral/personality traits such as novelty preference, impulsivity and anxiety. The present results show that considering the drug setting or the living environment alone when trying to decipher the nature of the gene x drug x environment interactions that promote the development of drug addiction in vulnerable individuals falls short of capturing the importance of experiential factors associated with the initial exposure to the drug. These factors themselves depend on the interaction between housing/living conditions and the drug setting. Beyond their support for a hitherto under-estimated role of non-pharmacological factors (*48*) in the vulnerability to progress from controlled to

compulsive drug taking, the present results suggest that initiating drug use from the "dark side" (*49*), i.e. through negative reinforcement-based self-medication (*5*), precipitates the development of addiction in vulnerable individuals.

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## Author contributions:

DB, JLH, NV, LMP and ED designed the experiments. NV, ABR and MF performed the experiment and/or the data analysis of experiment 1. NV, SA and MF performed the experiment and/or the data analysis of experiment 2. MP, ED and DB performed the experiment and/or the data analysis of experiment 3. LMP, LZ and CG performed the experiment and/or the data analysis of experiment 4. MF, MP, BJE & DB wrote the MS.

## Competing interests:

The authors have no financial disclosure or conflict of interest to report.

## Supplementary Materials:

Materials and Methods

Supplementary text

Figures S1-S8

References (##-##)

# Figures and figure legends.

### *Figure 1. Environmental enrichment differentially shapes the behavioral traits of vulnerability and resilience to addiction in rats.*

Enrichment of the housing environment (EE) exacerbates the contribution of sweetness preference to a multidimensional behavioral model of personality diminishing the contribution of anxiety, sign-tracking and reactivity to novelty **(A and B)**. These behavioral traits differed in their contribution to the three distinct, environment-dependent [EE vs SE: Chi2=8.43, $p<0.05$], pseudo-personality patterns identified from a cluster analysis [cluster x trait interaction: $F_{8,180}=14.373$, $p<0.0001$, $\eta p^2=0.39$], thereby suggesting a complex multidimensional interaction between the environmental conditions and behavioral traits of vulnerability versus resilience to addiction. Quantitatively, EE did not influence the sweetness preference of rats [main effect of group: $F_{1,46}<1$; session: $F_{3,138}=11.538$, $p<0.0001$, $\eta p^2=0.20$ and group x session interaction: $F_{3,138}=1.7583$, $p>0.05$] **(C)** nor their preference for novelty [main effect of group: $F_{1,41}=2.3124$, $p>0.05$] **(D)**. However, EE abolished the behavioral trait of resilience to addiction, namely high locomotor response to novelty (HR), in that EE rats showed a marked decrease in their locomotor reactivity to novelty as compared to SE rats [main effect of group: $F_{1,46}=19.274$, $p<0.0001$, $\eta p^2=0.30$; time: $F_{11,506}=102.16$, $p<0.0001$, $\eta p^2=0.69$; group x time interaction: $F(11,506)=1.5757$, $p>0.05$] **(E)**. Similarly, EE prevented the development of asymmetrical approach behavior, biased towards the CS, characteristically displayed by sign tracker rats raised in a SE during the exploitation phase of an AutoShaping task [SE, left panel: phase x approach response: $F_{1,23}=24.459$, $p<0.0001$, $\eta p^2=0.52$; EE, right panel: phase x approach response: $F_{1,23}=3.8233$, $p>0.05$] **(F).** EE influenced behavioral manifestations of anxiety on the elevated plus maze (EPM) **(G)** such that, despite spending a similar percentage of time in the open arms of an EPM [main effect of group: $F_{1,43}=1.472$, $p>0.05$], EE rats made more head dippings while on the open arms than did SE rats [main effect of group: $F_{1,43}=3.8447$, $p<0.05$, $\eta p^2=0.08$]. *: $p\leq0.05$.

### *Figure 2: Environmental enrichment decreases the propensity to acquire cocaine SA in addiction-resilient rats.*

EE rats showed a lower rate of acquisition of cocaine SA than SE rats [main effect of group: $F_{1,46}=4.8168$, $p<0.05$, $\eta p^2=0.10$; session: $F_{9,405}=200.63$, $p<0.0001$, $\eta p^2=0.82$ and group x session interaction: $F_{9,405}=3.0058$, $p<0.01$, $\eta p^2=0.06$] (**A**, left panel). This effect was not simply driven by a small number of the EE population that failed to acquire SA. In fact, more than 50% of rats in the EE group stayed below the SA acquisition criterion (median number of cocaine infusions set at each session) (**A**, right panel). The high responder (HR) phenotype, which was almost non-existent in the EE population, violating the expected distribution typically observed in SE rats [$Chi^2=15.41$, $p<0.0001$] (**B**, right panel), was the behavioral trait that best recapitulated the differential tendency to self-administer cocaine shown by EE rats [main effect of group: $F_{1,22}=7.1607$, $p<0.05$, $\eta p^2=0.25$; session: $F_{9,198}=138.78$, $p<0.0001$, $\eta p^2=0.86$ and group x session interaction: $F_{9,198}=3.7631$, $p<0.001$, $\eta p^2=0.15$] (**B**, left panel). EE also decreased the propensity of addiction-resilient, LNP rats, and rats with low reward sensitivity, LSP rats, to acquire cocaine SA [environment x phenotype x session interaction: $F_{9,162}=5.2896$, $p<0.0001$,

$\eta p^2$=0.23 and $F_{9,180}$=2.1008, p<0.05, $\eta p^2$=0.10, respectively]. Thus, LNP and LSP rats from the EE population received far fewer cocaine infusions than their SE counterparts [planned comparison: p<0.01 and p<0.05 respectively] (**C** and **D**, left panels), even though the qualitative nature of these traits was not influenced by housing condition [environment x phenotype interaction: $F_{1,18}$<1; environment x phenotype x time interaction: $F_{4,72}$=1.9406, p>0.05, **C**, right panel and environment x phenotype interaction: $F_{1,20}$=1.7919, p>0.05; environment x phenotype x time interaction: $F_{3,60}$<1, **D**, right panel]. *: p≤0.05.

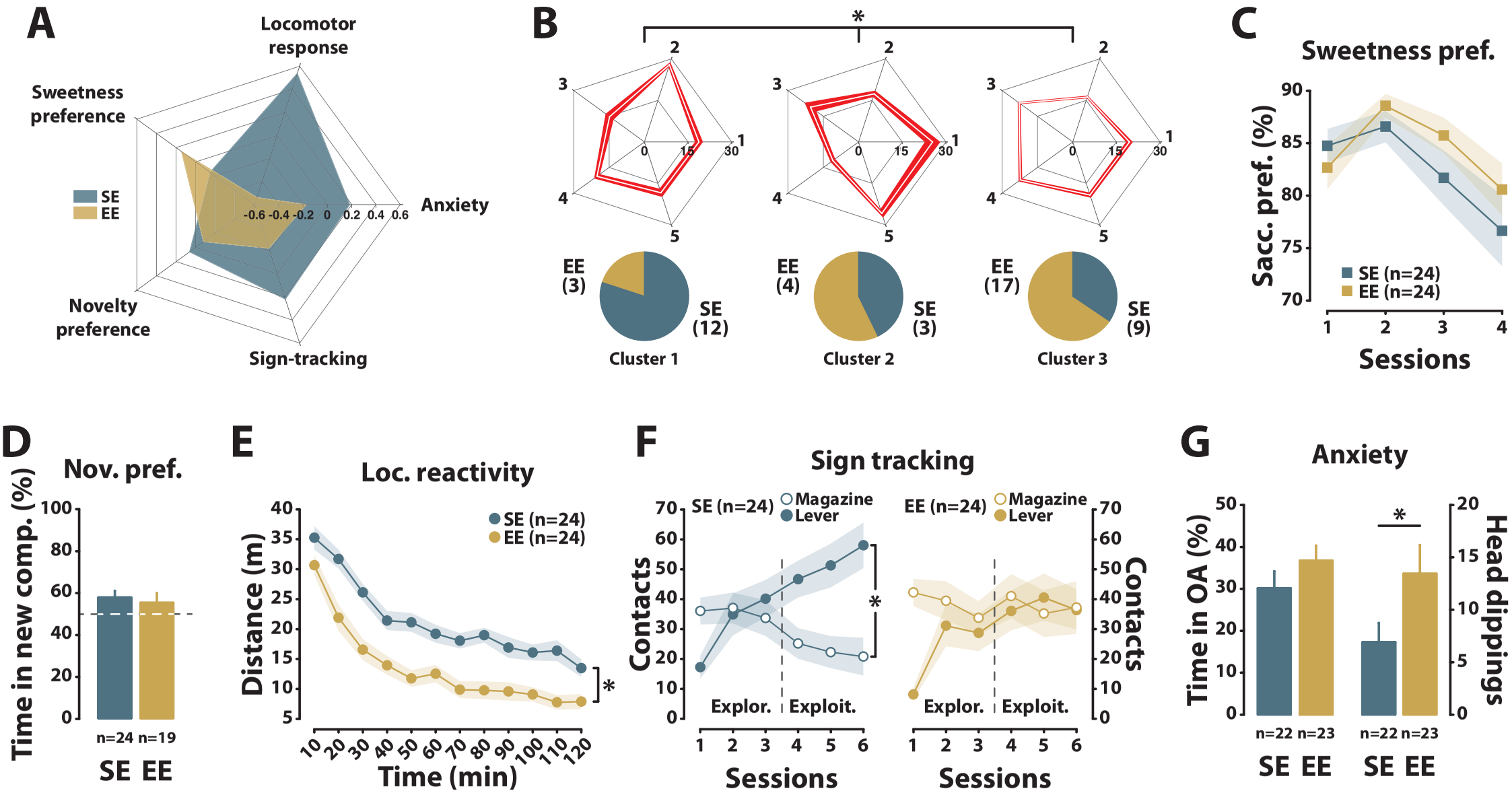
***Figure 3: A negative contrast between housing conditions (EE or SE) and drug taking setting promotes the development of cocaine addiction-like behavior.***

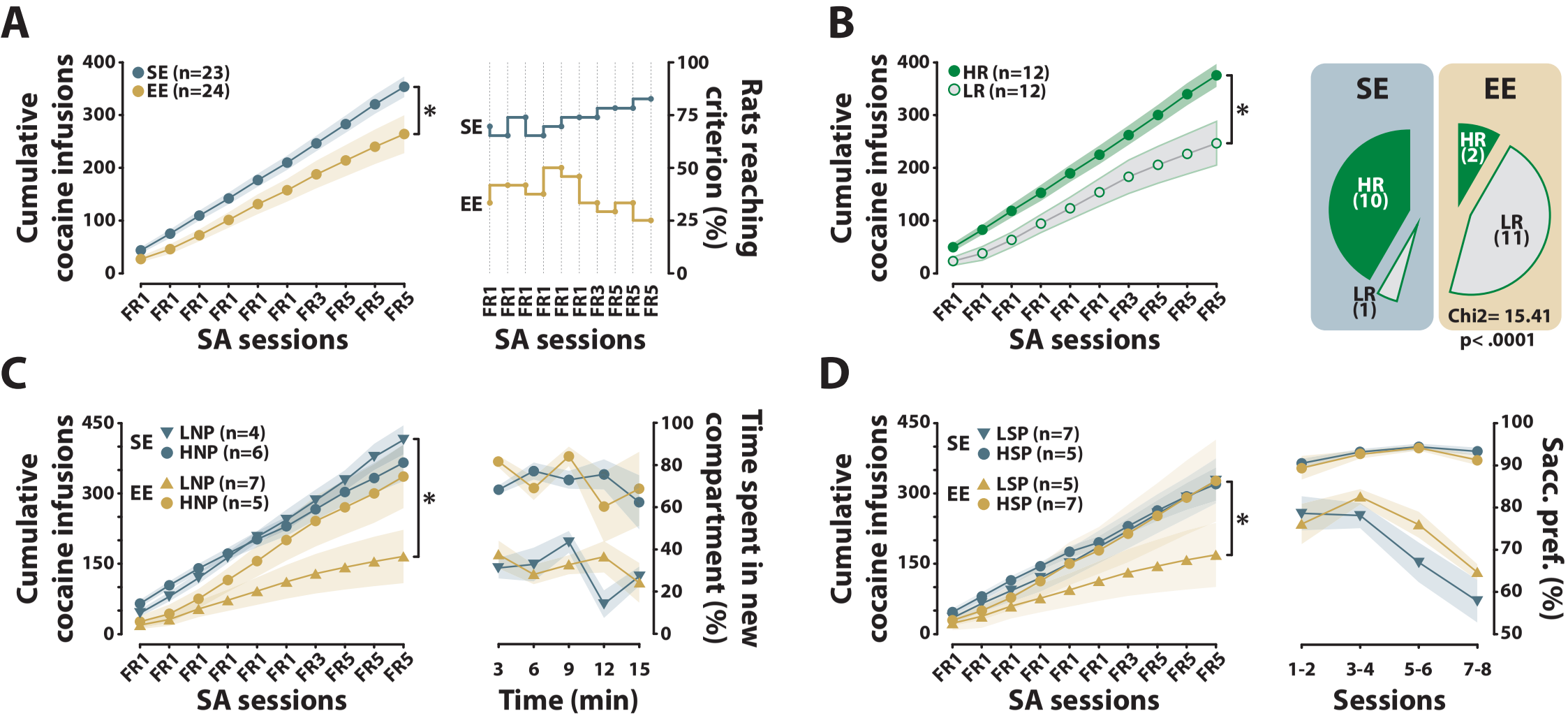
After 47 days of cocaine SA under a FR-5 schedule of reinforcement, rats from a heterogenous cohort comprising similar numbers of individuals housed in SE or EE were tested for the three behavioral criteria of addiction-like behavior: high motivation for the drug measured under progressive ratio; the maladaptive engagement in drug seeking, measured as the inability to refrain from responding when the drug is signaled as unavailable; the persistence of drug seeking despite negative consequences, measured as resistance to punishment. Rats were stratified on the number of criteria they displayed, i.e. 0, 1, 2 or 3 criteria (**A**). The 3crit group (n=5, 14% of the entire population) was the only one having an average addiction score that was outside the standard deviation of the overall population (grey bar). In contrast, the 0crit group (n=12, 33% of the overall population) was the only one displaying highly negative scores confirming their resilient phenotype [main effect of crit: $F_{3,32}$=17.955, p<0.0001, $\eta p^2$=0.63] **(A)**. The difference between these groups was not attributable to a differential exposure to cocaine throughout their SA history [main effect of crit: $F_{3,32}$<1]. However, retrospectively factoring housing conditions revealed that EE rats had significantly higher addiction scores than SE rats, the latter actually having negative scores [main effect of environment: $F_{1,34}$=8.8255, p<0.01, $\eta p^2$=0.21] **(B)**. All of the 3crit rats and the majority of 2crit rats were from the EE population, in clear contrast to the predominance of SE rats in the resilient, 0crit, population **(C)**. The higher addiction scores of EE rats as compared to SE rats were attributable to compulsivity [main effect of group: $F_{1,34}$=7.1942, p<0.05, $\eta p^2$=0.17] and persistence of responding when the drug was unavailable [main effect of group: $F_{1,34}$=4.5662, p<0.05, $\eta p^2$=0.12], but not to any differences in motivation [main effect of group: $F_{1,34}$=1.2117, p>0.05]. The facilitation of the transition to addiction by EE was not attributable to a differential exposure to cocaine or to a differential sensitivity to pain [main effect of environment: $Fs_{1,34}$<1] **(D)**. *: p≤0.05.

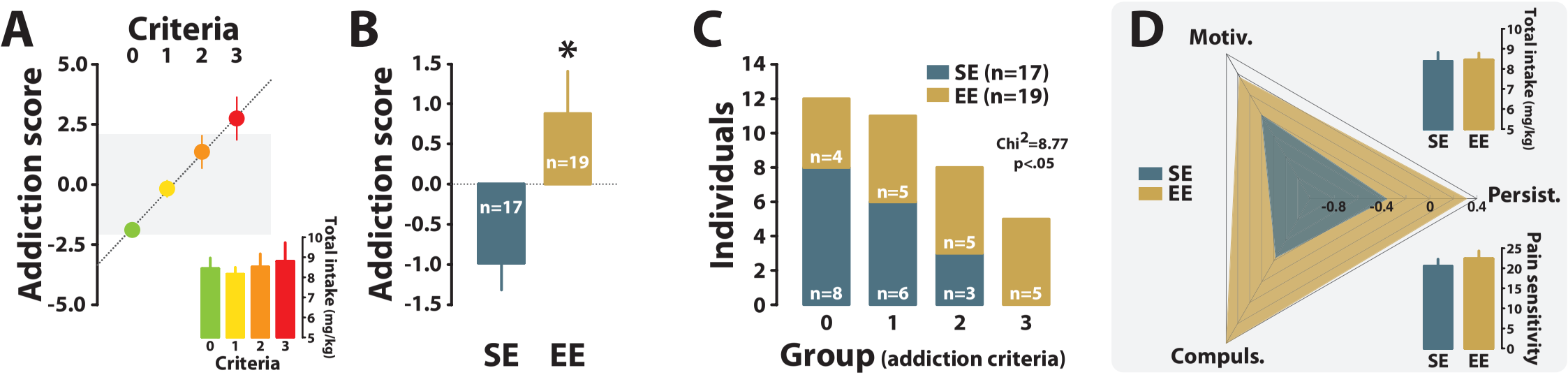
***Figure 4: Alcohol drinking in a negative experiential state induced either by negative environmental contrast or by the aversive nature of the drug setting promotes the development of compulsivity.***

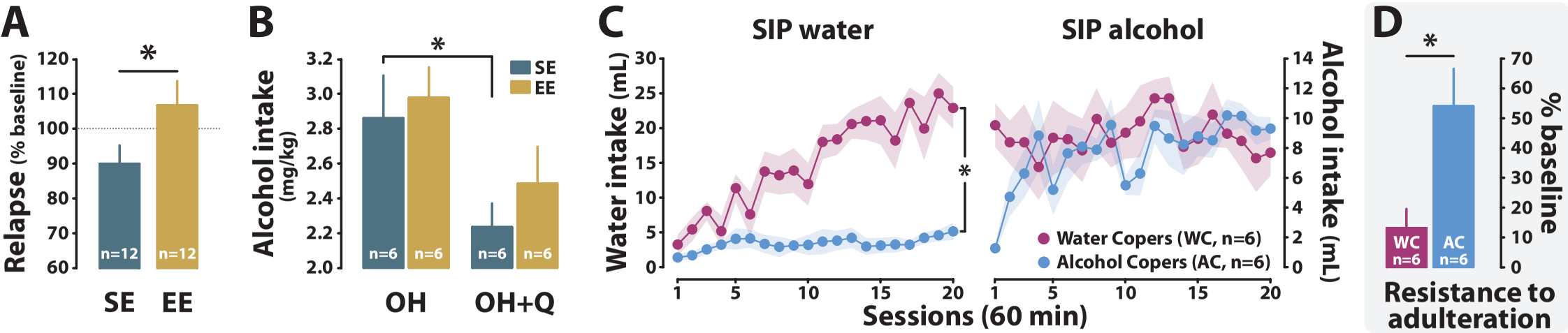
After 20 days of abstinence following a 3-month history of exposure to alcohol in an intermittent two-bottle choice procedure, EE rats were more prone to relapse to alcohol drinking than SE rats [Mann-Whitney: U=37.00, p<0.05] **(A)**. EE rats were also more prone to persist in drinking alcohol despite adulteration with quinine, thereby displaying compulsive drinking behavior [Kruskal-Wallis EE: $H_{1,12}$=2.08, p>0.05; SE: $H_{1,12}$=4.33,

$p<0.05$] **(B)**. In another cohort of outbred SE rats, introduction of the opportunity to drink alcohol as a means of coping with distress in a schedule-induced polydipsia procedure resulted in a specific subpopulation of individuals (Alcohol Copers, AC) that developed adjunctive alcohol drinking behavior [main effect of group: $F_{1,10}=1.2771$, $p>0.05$; session: $F_{19,190}=1.2348$, $p>0.05$; group x session interaction: $F_{19,190}=1.4429$, $p>0.05$; **C**, right panel] that they had failed to acquire when water was available, in marked contrast to rats that had acquired high levels of water intake (Water Copers, WC) [main effect of group: $F_{1,10}=33.619$, $p<0.001$, $\eta p^2= 0.77$; session: $F_{19,190}=9.8985$, $p<0.0001$, $\eta p^2=0.50$ and group x session interaction: $F_{19,190}=7.0845$, $p<0.0001$, $\eta p^2= 0.41$; **C**, left panel]. Although both WC rats and AC rats consumed the same amount of alcohol overall [main effect of group: $F_{1,10}=1.2771$, $p>0.05$], only the latter, i.e. those that had acquired a coping strategy by drinking alcohol, subsequently displayed compulsive alcohol drinking, being resistant to adulteration of alcohol with quinine [main effect of group: $F_{1,10}=8.3820$, $p<0.05$, $\eta p^2=0.46$] **(D)**. *: $p\leq0.05$.


A
Locomotor response
Sweetness preference
Anxiety
Novelty preference
Sign-tracking
SE
EE
-0.6 -0.4 -0.2 0 0.2 0.4 0.6
B
*
EE (3)
SE (12)
Cluster 1
EE (4)
SE (3)
Cluster 2
EE (17)
SE (9)
Cluster 3
C
Sweetness pref.
Sacc. pref. (%)
SE (n=24)
EE (n=24)
Sessions
D
Nov. pref.
Time in new comp. (%)
n=24 n=19
SE EE
E
Loc. reactivity
Distance (m)
SE (n=24)
EE (n=24)
Time (min)
F
Sign tracking
SE (n=24)
Magazine
Lever
EE (n=24)
Contacts
Explor.
Exploit.
Sessions
G
Anxiety
Time in OA (%)
Head dippings
n=22 n=23
n=22 n=23
SE EE
SE EE


A
Cumulative cocaine infusions
SE (n=23)
EE (n=24)
*
SA sessions
Rats reaching criterion (%)
SE
EE
B
HR (n=12)
LR (n=12)
HR (10)
LR (1)
HR (2)
LR (11)
Chi2= 15.41
p< .0001
C
SE
LNP (n=4)
HNP (n=6)
EE
LNP (n=7)
HNP (n=5)
Time spent in new compartment (%)
Time (min)
D
LSP (n=7)
HSP (n=5)
LSP (n=5)
HSP (n=7)
Sacc. pref. (%)
Sessions


A
Criteria
0 1 2 3
Addiction score
5.0
2.5
0.0
-2.5
-5.0
Total intake (mg/kg)
10 9 8 7 6 5
0 1 2 3
Criteria
B
Addiction score
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
*
n=17
n=19
SE EE
C
Individuals
14 12 10 8 6 4 2 0
SE (n=17)
EE (n=19)
Chi2=8.77
p<.05
n=4
n=8
n=5
n=6
n=5
n=3
n=5
0 1 2 3
Group (addiction criteria)
D
Motiv.
Persist.
Compuls.
SE
EE
-0.8 -0.4 0 0.4
Total intake (mg/kg)
10 9 8 7 6 5
SE EE
Pain sensitivity
25 20 15 10 5 0
SE EE


A
Relapse (% baseline)
120
110
100
90
80
70
60
*
n=12
n=12
SE
EE
B
Alcohol intake (mg/kg)
3.2
3.0
2.8
2.6
2.4
2.2
2.0
*
SE
EE
n=6
n=6
n=6
n=6
OH
OH+Q
C
SIP water
SIP alcohol
Water intake (mL)
30
25
20
15
10
5
0
*
Alcohol intake (mL)
14
12
10
8
6
4
2
0
Water Copers (WC, n=6)
Alcohol Copers (AC, n=6)
1
5
10
15
20
Sessions (60 min)
D
*
% baseline
70
60
50
40
30
20
10
0
WC n=6
AC n=6
Resistance to adulteration