Greater sensitivity to novelty in rats is associated with increased motor impulsivity following repeated exposure to a stimulating environment: implications for the etiology of impulse control deficits

Jacqueline-Marie N. Ferland,1,* Fiona D. Zeeb,1,*† Katrina Yu,1 Sukhbir Kaur,1 Matthew D. Taves2 and Catharine A. Winstanley1

1Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC, V6T 1Z4, Canada
2Department of Zoology, University of British Columbia, Vancouver, BC, Canada

Keywords: addiction, environmental enrichment, hippocampus, hyperactivity, individual differences

Abstract

Heightened motor impulsivity and increased novelty-seeking commonly co-occur in psychiatric disorders, including drug addiction. However, the relationship between these two phenomena remains unclear. One-time tests of novelty sensitivity commonly used in preclinical experiments, such as the open-field or novel-object test, fail to capture the fact that novelty-seekers repeatedly experience novel, stimulating situations. The present study therefore investigated whether repeated exposure to a novel, stimulating environment (SE) altered impulsive action. Male Long-Evans rats were trained to perform the five-choice serial reaction time task (5CSRTT) which measures motor impulsivity in the form of premature responding as well as attention and motivation. Animals were then exposed to a novel SE (1 h/day for 16 days) immediately prior to the 5CSRTT. Significant increases in premature responding were observed in a subgroup of reactive animals termed high responders (HR-SE). These rats were not more impulsive at baseline, and levels of impulsivity normalised once exposure to the SE was discontinued. No other aspect of 5CSRTT performance was affected by the SE challenge. We also determined that HR-SE rats were hyperactive in a novel environment. Biochemical analyses revealed changes in gene and protein expression within the dorsal hippocampus of HR-SE rats, including decreases in mRNA encoding the dopamine D1 receptor and brain-derived neurotrophic factor. These results indicate a novel mechanism by which impulsivity and novelty-reactivity interact that may enhance addiction vulnerability synergistically. Furthermore, studying such context-induced impulsivity may provide insight into the process by which environmental load precipitates psychiatric symptoms in impulse control disorders.

Introduction

Abnormally high rates of motor impulsivity, characterised by an inability to withhold a response, are present in several psychiatric disorders including pathological gambling and substance abuse (Evenden, 1999; Fillmore & Rush, 2002; de Wit, 2009; Fox et al., 2010; Brevers et al., 2012). Heightened motor impulsivity may also influence the ‘loss of control’ associated with drug-seeking, continuous gambling, and other risky behaviours (Colder & O’Connor, 2002; Billieux et al., 2010; Brevers et al., 2012). Likewise, highly impulsive rats self-administer more cocaine and demonstrate an increased susceptibility to relapse (Dalley et al., 2007; Economidou et al., 2009).

Sensation- or novelty-seeking has been associated with addiction and a heightened propensity to relapse in both human and animal studies (Belin & Deroche-Gamonet, 2012; Evren et al., 2012; Tomassini et al., 2012; Vidal-Infer et al., 2012). Preclinical paradigms including the open-field test, novel-object test, and locomotor activity in a novel environment are used as one-time screens to detect animals that show a greater sensitivity to a novel environment (novelty reactivity). In rats, exposure to a novel environment initially stimulates locomotor activity which quickly declines as animals habituate (Feigley et al., 1972). However, for a subgroup of individuals (high responders), locomotor activity is potentiated, habituates at a slower rate, and is accompanied by elevated corticosterone (Piazza et al., 1991). These animals show an increased tendency to self-administer addictive substances (Piazza et al., 1991). Individual differences in novelty reactivity may therefore provide some insight into the novelty-seeking trait.
Interestingly, high novelty reactivity in rats, indicated by a single locomotor activity test, predicted a lack of behavioural inhibition, a type of impulsive behaviour (Stoffel & Cunningham, 2008). However, rats screened for high or low levels of impulsive action, as measured by premature responses made on the five-choice serial reaction-time task (5CSRTT), did not differ in spontaneous locomotor activity in a novel environment (Molander et al., 2011). Although both motor impulsivity and the response to novelty are associated with addiction vulnerability, it is therefore unclear whether these traits operate independently or synergistically. However, one aspect of this question that has not been thoroughly considered is the way in which exposure to a novel environment influences impulsive behaviour in novelty-seeking subjects. Interacting with novel objects and environments can induce a cascade of neurobiological signals, some of which are implicated in the regulation of impulse control (see Hall & Perona, 2012). A heightened response to novelty may therefore precipitate impulsivity, potentially facilitating engagement in risky behaviours involving substance use. Although trait levels of impulsive action appear stable in adult animals (see, e.g., Dalley et al., 2007), it is unknown whether impulsivity can be modified by repeated exposure to a stimulating environment (SE), somewhat mimicking the actual behaviour of novelty-seekers (Cloninger et al., 1993).

To address this question, rats were exposed to a SE 1 h prior to testing on the 5CSRTT for 16 days, after which gene and protein expression in key brain regions implicated in motor impulsivity were analysed. We also determined whether increased locomotor activity in a novel environment could predict changes in impulse control caused by exposure to the SE.

Materials and methods

Subjects

The experiment used two cohorts of 16 male Long–Evans rats (Charles River Laboratories, St Constant, Canada), run in series. Rats weighed between 275 and 300 g upon arrival and were maintained at ~85% of their free-feeding weight by restricting their food to ~14 g of rat chow per day. Water was available ad libitum. Animals were housed in pairs under a reversed 12-h light–dark cycle (lights off at 08.00 h) in a temperature-controlled colony room maintained at 21 °C. Testing and housing were in accordance with the Canadian Council of Animal Care, and all experimental protocols were approved by the Animal Care Committee of the University of British Columbia.

Behavioural apparatus and training

Behavioural testing for the 5CSRTT was conducted in eight standard five-hole operant chambers enclosed within ventilated sound-attenuating cabinets (Med-Associates, Inc., Vermont, USA). One wall of each chamber consists of an array of five response holes. The food magazine, positioned 2 cm above the bar floor located opposite to the response holes, was attached to an external food dispenser equipped to deliver sucrose pellets (45 mg; Bioserv, New Jersey, USA) to the magazine. A light stimulus was situated at the back of each response hole as well as within the food magazine. Nosepoke responses into these apertures were detected by a horizontal infrared beam. Chambers could be illuminated by a houselight, and were controlled by software, written in Med PC by C.A.W., running on an IBM compatible computer.

Animals (n = 32) were first habituated to the operant chambers over two daily 30-min sessions during which sucrose pellets were placed in the response holes and food magazine. As described in detail in previous publications (Winstanley et al., 2003), animals were trained to respond in one of the five holes when the stimulus light located in the back of the response aperture was briefly illuminated (0.5 s). The stimulus light could appear in any of the five holes, and the spatial location of the target was varied randomly from trial to trial. Each session consisted of 100 trials and lasted ~30 min. Animals initiated each trial by making a nosepoke response at the food tray. There was then a 5-s intertrial interval (ITI) during which animals had to withhold from making a response at the array before the stimulus light was presented. Premature or impulsive responses made at the array during the ITI were followed by a 5-s time-out period during which the houselight was turned on and no further trials could be initiated. A correct response at the illuminated hole was rewarded with delivery of one sugar pellet in the food tray. Food delivery was signalled by illumination of the traylight, which remained on until the animal collected the reward. An incorrect or lack of response (omission) was not rewarded and was followed by the same time-out as premature responses. Repeated responding at the correct hole following a correct response was classified as perseverative responding and, while monitored, did not lead to a time-out. Animals were trained for five or six sessions per week until stable performance was reached (≥80% accuracy, ≤20% omissions). This took ~55 sessions.

Locomotor testing

Locomotor activity in a novel environment was assessed in the second cohort of animals (n = 16) prior to the start of the 5CSRTT training. Locomotor activity was measured in boxes similar to those described above (Med-Associates, VT, USA), but lacked the response aperture array. Although a food magazine and an external food dispenser were present, no reward was delivered at any time. Boxes were equipped with four horizontal infrared beams, located ~5 cm from the grid floor, running from the front to the rear of the chamber. The degree of locomotor activity was measured by the number of beam breaks recorded within a single 60-min session, parsed into 20-min bins for analysis. The locomotor boxes were controlled by software written in Med PC by Dr Stan B. Floresco on an IBM-compatible computer.

SE procedure

Once stable performance on the 5CSRTT was achieved (see Data Analyses section), each cohort of rats was divided into two groups (n = 8 per group) matched for their level of accuracy, premature responding, response latencies, omissions, trials completed and perseverative responding on the 5CSRTT. Additionally, as all rats were pair-housed, animals in each cage were always in the same cohort. During the first SE challenge, one group was placed into a large enrichment cage (Corners Limited, Kalamazoo, MI, USA) for 1 h immediately prior to behavioural testing, while the other group remained in the pair-housed environment. This process was maintained for 16 days and followed by 3 days during which animals remained in their home cages and subsequently five non-enriched 5C5RTT test days (Post-SE). The designation of the groups was then reversed such that the previously challenged group remained pair-housed and the SE procedure was repeated with the previously pair-housed group to expose all rats to the SE. A schematic summarising the experimental design is provided in Fig. 1.
The enrichment cage consisted of a large custom mesh cage measuring 102 × 152 × 76 cm with solid plexiglass flooring. The cage contained stimulating materials such as tubes, chains, novel toys, various sizes of tunnels, buckets and paper towels for the animals to interact with. Plexiglass shelves (one large measuring 60 × 19 cm and four small measuring 38 × 14 cm) were also attached to the walls of the cage at varying locations, elevations and angles to provide raised platforms for the animals to explore. To maintain a highly stimulating and novel environment each day, all SE materials were adjusted daily.

Ex vivo analyses

Once the behavioural experiment had been completed, animals remained pair-housed in the colony room for 5–7 days prior to being killed by live decapitation. Each cohort of 16 rats were killed over 2 days. On each day, six rats were placed in the SE cage for a minimum of 1 h prior to being killed and two control rats remained in their home cages. All rats were killed within 3 min of being removed from their cage. Following decapitation, trunk blood was collected and stored at 4 °C overnight for corticosterone analysis. The brain was rapidly removed and sliced into 1-mm sections using a chilled brain matrix. Bilateral tissue samples from the orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), nucleus accumbens (NAC), dorsal striatum (caudate putamen, CPU), basolateral amygdala (BLA) and the dorsal hippocampus (dHPC) were then dissected, immediately frozen on dry ice, and stored at −80 °C.

Blood corticosterone analysis

Total blood corticosterone concentrations of all rats were quantified using a commercial radioimmunoassay kit (MP Biomedicals, Solon, OH, USA, no. 07120103). Chilled trunk blood was centrifuged for 15 min at 4 °C and the serum supernatant (1.0 mL/rat) was transferred into fresh tubes and stored at −20 °C until radioimmunoassay. Thawed serum samples were then diluted in steroid diluent and assayed as previously described (Brunnmette et al., 2010). Tubes were counted for 1 min in a gamma counter, and the detection limit was 3.12 pg per tube.

Brain tissue analysis

Brain tissue samples from the first cohort were subjected to real-time quantitative polymerase chain reaction (RT-qPCR) analysis to determine changes in messenger ribonucleic acid (mRNA) expression. Samples from the second cohort were analysed by Western blotting to detect differences in protein levels.

RNA isolation and cDNA synthesis for RT-qPCR analysis

Brain tissue samples from the first cohort were subjected to RNA isolation using Trizol reagent (Invitrogen, Carlsbad, CA, USA; cat. no. 15596-018) following the manufacturer’s protocol. Final mRNA concentrations were determined by a NanoDrop spectrophotometer (Nanodrop, Wilmington, DE, USA) which was also used to confirm the purity and quality of the mRNA obtained. Samples were then stored at −80 °C until complementary DNA (cDNA) synthesis.

Before cDNA synthesis, all samples underwent DNA removal to ensure mRNA remained uncontaminated (DNA-free Kit; cat. no. AM1906; Applied Biosystems, Carlsbad, CA, USA). Following completion of this protocol, all samples were subjected to cDNA synthesis in which 10 μL of DNAse-treated RNA was diluted 2× by mixed manufacturer cDNA synthesis solution (Invitrogen High Capacity cDNA Reverse Transcription Kit; PN 4368814). All samples were placed in a standard RNA-free PCR plate (Applied Biosystems; PN 403012 and PN 4360954) and underwent cDNA synthesis in an Applied Biosystems StepOne Plus real-time PCR machine. All synthesised cDNA was stored at −20 °C until RT-qPCR analysis.

RT-qPCR

cDNA samples were diluted 10× in water, with the exception of samples taken from the NAC and BLA which were subjected to a 1/1.66 cDNA dilution to maintain the integrity of the sample despite the smaller volume of tissue obtained. While storing all diluted samples on ice, gene primer mixes were combined according to the manufacturer’s instructions such that there was 0.8 μL of gene primer per mix. We chose to target genes known to be involved in memory formation, neuronal activation, the stress response, receptor activity and neuronal development. Analyses were conducted on tissue samples from areas previously demonstrated to be important in the regulation of novelty reactivity and 5CSRTT performance. Specifically, we analysed expression of Arc, cFos, corticotrophin releasing factor (CRF) 1 receptor (CRF1), cAMP response element-binding protein (CREB), brain-derived neurotrophic factor (BDNF), dopamine (DA) DA D1 and DA D2 receptors, and serotonin (5-hydroxytryptamine; 5-HT1A and 5-HT2A receptors (see Table 1 for primer sequences). RT-qPCR analyses were performed using an Applied Biosystems StepOne Plus real-time PCR machine. Each sample was run in triplicate.

Western blotting

Using a RIPA buffer (SDS, 10%; IGEPAL, 1%; Sarkosy, 0.5%; NaCl, 150 mM; Tris base, 50 mM; and standard protease inhibitor), tissue was homogenised in a 3 : 1 buffer-to-tissue ratio. Protein concentration and purity were assessed using a NanoDrop spectrophotometer. Remaining homogenised tissue was stored at −20 °C before sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) assay.

Samples were thawed at room temperature and combined with Laemmli sample buffer using a 1 : 1 ratio (BioRad, Mississauga,
Ontario, Canada). Samples were loaded onto polyacrylamide gel in running buffer (1× Tris glycine solution) and run at 110 V for 2 h. A protein ladder was included in each gel as a control for protein movement. Gels were run again through a resolving layer at 110 V to complete protein movement.

Following SDS-PAGE, proteins on gels were transferred onto blotting paper and placed into transfer buffer (methanol and Tris-glycine). Once proteins had been transferred, blots were blocked using 5% milk in 1× TBS with 1% Tween solution. Gels were then incubated overnight with primary and secondary antibodies for the following proteins: DA D1 receptor, BDNF, 5-HT2A receptor, CREB, phosphorylated CREB (pCREB), extracellular signal-regulated kinase (ERK) and β-tubulin as a control (see Table 2 for specific primary antibodies; secondary antibody used for DA D1 receptor, BDNF, 5-HT2A receptor, CREB, phosphorylated CREB (pCREB), extracellular signal-regulated kinase (ERK) and β-tubulin used a 1:10 000 dilution IRDye 800 CW Goat anti-mouse monoclonal, Santa Cruz, SC-50397 clone MK12, Millipore, cat. no. 05-1152 0.2 μg/mL clone AA2 mouse monoclonal, Millipore, cat. no. 05-661

Table 2. Primary antibodies used for Western blot analyses

<table>
<thead>
<tr>
<th>Protein</th>
<th>Primary antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 receptor</td>
<td>1 : 200 dilution rabbit polyclonal primary antibody, Santa Cruz, cat. no. SC14001</td>
</tr>
<tr>
<td>5-HT2A receptor</td>
<td>1 : 200 dilution rabbit polyclonal, Santa Cruz, SC-50397</td>
</tr>
<tr>
<td>BDNF</td>
<td>1 : 200 dilution rabbit polyclonal, Santa Cruz, cat. no. SC-20981</td>
</tr>
<tr>
<td>CREB</td>
<td>1 : 1000 dilution mouse monoclonal, Cell Signalling, cat. no. 86B10</td>
</tr>
<tr>
<td>pCREB</td>
<td>1 : 1000 dilution mouse monoclonal anti-phospho CREB (ser133), Millipore, cat. no. 06-519</td>
</tr>
<tr>
<td>ERK</td>
<td>1 : 1000 dilution Mouse monoclonal anti-ERK ½ (p44/1p42) clone MK12, Millipore, cat. no. 05-1152</td>
</tr>
<tr>
<td>β-tubulin (control)</td>
<td>0.2 μg/mL clone AA2 mouse monoclonal, Millipore, cat. no. 05-661</td>
</tr>
</tbody>
</table>

Data analyses

All data analyses were performed using SYStat 12.0 software (Chicago, IL, USA) as described in detail in previous reports (Winstanley et al., 2003; Winstanley, 2007). Data was pooled for both cohorts for 5CSRTT analyses and the following variables were analysed: percentage accuracy (number of correct responses / total correct and incorrect responses × 100); percentage of responses omitted (number of omissions/total number of correct, incorrect and omitted responses × 100); percentage of premature responses (number of premature responses/total number of trials initiated × 100), latency to make a correct response, latency following an incorrect response, latency to collect reward, sum of perseverative responses made and trials completed. Variables expressed as a percentage were subjected to an arcsine transformation in order to limit the effect of an artificially imposed ceiling (i.e. 100%; McDonald, 2009). Data from the last five baseline sessions prior to the SE challenge were analysed using repeated-measures ANOVA with Session (five levels) as a within-subjects factor. Performance was deemed stable if there was no main effect of session in any of the behavioural parameters across the full cohort. Data from one subject was excluded from all analyses as the criterion level of accuracy on the 5CSRTT was never achieved (> 80% correct).

Designation of subgroups

Upon reviewing 5CSRTT data during the SE challenge, it became clear that substantial individual differences were present with respect to the number of premature responses made. Rats (n = 31) were therefore divided into two groups, termed high or low responders to the SE (HR-SE and LR-SE respectively), based on a post hoc analysis of this change in premature responding, as exemplified in the final five sessions of exposure to the SE. To be classified as HR-SE, the level of premature responding observed had to be (i) ≥ 50% of an individual’s baseline performance, and (ii) greater than the average of the whole group (calculated by the average of the last five stable baseline sessions prior to the SE challenge). Animals were classified as LR-SE if they did not meet these criteria. Between the two cohorts, 10 out of 31 rats met criteria for the HR-SE group. To ensure these criteria did not select animals with naturally fluctuating levels of premature responding, identical analyses were used to determine whether changes from baseline on all non-SE days (i.e. in which animals were tested in the 5CSRTT but remained pair-housed) revealed any HR-nonSE animals. This analysis found no subjects matching these conditions (data not shown), thus suggesting that the increase in impulsivity observed in the HR-SE subgroup was specific to, and triggered by, SE exposure. To compare the difference between HR-SE and LR-SE groups, the between-subjects factor Group (two levels) was included in all subsequent analyses.

Locomotor activity was analysed using ANOVA with group as a between-subjects factor and bin (three levels: 0–20 min, 20–40 min, 40–60 min) as a within-subjects factor. Sum of total locomotion was also analysed using ANOVA with group as a between-subjects factor. Blood serum corticosterone data was subject to a one-way ANOVA with group as a between-subjects factor. RT-qPCR results were analysed using the ΔΔCt method. All PCR data were normalised to levels

Table 1. Oligonucleotide sequences for primers targeted in RT-qPCR analyses

<table>
<thead>
<tr>
<th>Primer gene</th>
<th>Forward sequence</th>
<th>Reverse sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>REB</td>
<td>ATCGTGCACTTCTGGTATGATC</td>
<td>GGGAGGAGGCCATAAACAATC</td>
</tr>
<tr>
<td>BDNF</td>
<td>AAGGGCAGTAGGACCTGGCAAT</td>
<td>TTAAGAAGCCGCCACCAATT</td>
</tr>
<tr>
<td>D1 receptor</td>
<td>GGCTTTCTGGGCCCTTTTTT</td>
<td>ATCAGCGAGGGTCAGAAATGG</td>
</tr>
<tr>
<td>D1 receptor</td>
<td>TAAGACGATAGGCCCGCAGAA</td>
<td>TGAACACAAGCGGAAATAGG</td>
</tr>
<tr>
<td>5-HT2A receptor</td>
<td>TACTCCACTTTGGCGCGTTT</td>
<td>AGGGTGCGGCGCTCTGAAG</td>
</tr>
<tr>
<td>5-HT2A receptor</td>
<td>CCTCAGCACCACGCAACAAAC</td>
<td>TGGACCGTGCCTGCCCGCTTA</td>
</tr>
<tr>
<td>cFos</td>
<td>GGAATTAAACCTGGTCTGCGGA</td>
<td>TGACATGGACGCGCTAG</td>
</tr>
<tr>
<td>Arc</td>
<td>TGGTTGGAGGTCTAAGAAGGA</td>
<td>TCTGTAAGTACGGCCTCCCTTA</td>
</tr>
<tr>
<td>CRF1</td>
<td>ATCGCGGTCCTGAGAAACAT</td>
<td>GTAGACTGGACCACAAACCA</td>
</tr>
</tbody>
</table>

© 2014 Federation of European Neuroscience Societies and John Wiley & Sons Ltd
European Journal of Neuroscience, 1–11
of the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) according to the following formula: \( \Delta Ct = Ct \text{ (gene of interest}) - Ct \text{ (GAPDH).} \) Adjusted expression levels for HR-SE animals were calculated relative to their LR-SE animals as follows: \( \Delta \Delta Ct = \Delta Ct \text{ (HR-SE) – } \Delta Ct \text{ (LR-SE).} \) In keeping with recommended practice in the field (Livak & Schmittgen, 2001), expression levels relative to LR-SE were then calculated using the following expression: \( 2^{-\Delta \Delta Ct}. \) After these calculations, mean group results were analysed using an independent-samples t-test with group as a between-subjects factor. Levels of protein expression detected by Western blot were analysed using an independent-samples t-test with group as a between-subjects factor. It was found that data from the LR-SE animals kept in home cages prior to killing did not differ significantly from those placed in the enrichment cage (all \( t_{14} < 3.28, \ P > 0.08 \)), and results were therefore pooled for all ex vivo analyses.

For all analyses, results were deemed to be significant if \( P \)-values were less than or equal to an alpha of 0.05. Analyses yielding a \( P \)-value between 0.05 and 0.08 are reported as a trend.

Results

Premature (impulsive) responding

Substantial individual differences were clearly present in the degree of premature responding observed following repeated SE exposure. Animals categorised as HR-SE (see statistical methods for details) exhibited a significant increase in premature responding on the 5CSRRT (sessions 1–16: session, \( F_{1,29} = 2.202, \ P = 0.006; \) session \( \times \) group, \( F_{1,20} = 5.744, \ P = 0.02 \)). During the first 4 days of SE, premature responding was variable, suggesting that the SE was impacting animals’ performance, but no differences were detected between HR-SE and LR-SE rats during these initial sessions (Fig. 2A; sessions 1–4 group, \( F_{1,29} = 2.66, \ P = 0.11; \) session, \( F_{3,87} = 4.46, \ P = 0.006; \) session \( \times \) group, \( F_{1,29} = 0.247, \ P = 0.86 \)). During sessions 5–12 a group effect started to develop, illustrating a difference between HR-SE and LR-SE rats in their response to the SE (group: sessions 5–8, \( F_{1,29} = 3.39, \ P = 0.08; \) sessions 9–12, \( F_{1,29} = 3.36, \ P = 0.08 \)). The emergence of a significant session \( \times \) group interaction indicated that premature responding was increasing in HR-SE but not LR-SE rats (sessions 5–8: session, \( F_{3,87} = 0.52, \ P = 0.67; \) session \( \times \) group, \( F_{3,87} = 1.04, \ P = 0.38; \) sessions 9–12: session, \( F_{3,87} = 0.52, \ P = 0.67; \) session \( \times \) group, \( F_{3,87} = 4.30, \ P = 0.007 \)).

During the final four SE sessions, the number of premature responses stabilised and HR-SE rats made significantly more of these impulsive responses than did LR-SE rats (sessions 13–16: group, \( F_{1,29} = 12.70, \ P = 0.001; \) session, \( F_{3,87} = 0.83, \ P = 0.48; \) session \( \times \) group, \( F_{3,87} = 0.59, \ P = 0.62 \)). Together, these data suggest that repeated exposure to SE elevated levels of motor impulsivity in some individuals. Critically, premature responding did not differ between HR-SE and LR-SE animals at baseline, prior to the SE challenge (group, \( F_{1,29} = 1.00, \ P = 0.32 \) or once exposure to the SE ceased (Post-SE sessions 1–5: group, \( F_{1,29} = 1.82, \ P = 0.19; \) session, \( F_{4,116} = 2.15, \ P = 0.08; \) session \( \times \) group, \( F_{4,116} = 1.29, \ P = 0.28 \)). The increase seen in the last 5 days of SE was significantly higher than the baseline and post-SE sessions (baseline average vs. last 5 SE average: group, \( F_{1,29} = 5.82, \ P = 0.02; \) session, \( F_{1,29} = 40.09, \ P = 0.000; \) session \( \times \) group, \( F_{2,58} = 36.58, \ P = 0.000; \) last 5 SE average vs. Post-SE average: group, \( F_{1,29} = 6.52, \ P = 0.01; \) session, \( F_{1,29} = 0.66, \ P = 0.42; \) session \( \times \) group, \( F_{1,29} = 11.03, \ P = 0.002 \)), indicating that SE exposure unmasked a pro-impulsive tendency that would otherwise not be manifest.

Furthermore, a difference was no longer observed between the number of premature responses made by HR-SE and LR-SE rats; the heightened impulsive action demonstrated by HR-SE rats was only present immediately following interaction with the SE, confirming the causal role played by the environmental challenge in the resulting behavioural disinhibition.

Other variables

In contrast to the effect of exposure to the SE on motor impulsivity, the accuracy of target detection was not altered in either group during the SE challenge (Fig. 2B; sessions 1–16: group, \( F_{1,29} = 0.22, \ P = 0.64; \) session, \( F_{15,435} = 1.04, \ P = 0.41; \) session \( \times \) group, \( F_{15,435} = 0.65, \ P = 0.83 \)). Likewise, omitted trials also did not differ by group (Fig. 2C; sessions 1–16: group, \( F_{1,29} = 0.16, \ P = 0.70; \) session \( \times \) group, \( F_{15,435} = 0.93, \ P = 0.53 \)). While the percentage of omissions varied significantly during the course of the SE challenge (sessions 1–16, \( F_{15,435} = 4.05, \ P = 0.000 \)), this effect was driven by

![Fig. 2. Exposure to an SE significantly and selectively increased impulsivity in a subgroup of high responders (HR-SE) on the 5CSRRT. (A) Premature responding significantly increased during the course of SE exposure in the HR-SE group, whereas this form of motor impulsivity remained unchanged in the low responding animals (LR-SE). The difference between HR-SE and LR-SE rats emerged after 5 days and was greatest during the last 4 days of SE exposure. There was no significant difference between HR-SE and LR-SE animals prior to the start of the SE challenge, and group differences were no longer evident once exposure to the SE ceased. (B) Both LR-SE and HR-SE rats maintained high levels of accuracy throughout SE exposure, and no significant differences were observed between the groups at any time point. (C) Although some variation was evident, there was no difference between HR-SE and LR-SE rats in the percentage of trials omitted. Data are presented as mean ± SEM. *\( P < 0.05; \) **\( P < 0.08 \).](image-url)
one HR-SE animal’s high level of omitted responses and was not reflective of the cohorts’ behaviour as a whole. No other variables were affected by exposure to the SE (Table 3; all \( F_{1.29} < 0.75, P > 0.40 \)).

Similarly, analysis of 5CSRTT performance prior to SE exposure confirmed that HR-SE and LR-SE rats did not differ on any behavioural measure at baseline (Table 3 and Fig. 2 accuracy: \( P = 0.40 \)). Therefore, the increase in premature responding observed in HR-SE rats following SE exposure could not be predicted by individual differences in any premorbid behavioural measure, and did not arise through a general disruption in task performance.

**Locomotor activity**

Following the discovery of HR-SE and LR-SE subgroups in the first cohort, we conducted a one-time screen of novelty-reactivity in the second cohort of rats prior to the start of 5CSRTT training. HR-SE animals (\( n = 4 \)) showed significantly higher levels of locomotor activity than did LR-SE rats overall (Fig. 3; 0–60 min: group, \( F_{1.14} = 8.37, P = 0.01 \); time bin, \( F_{5.70} = 25.92, P < 0.000 \); total locomotion, \( F_{1.14} = 8.37, P = 0.01 \)). The greatest differences occurred during the first 40 min (0–20 min: group, \( F_{1.14} = 6.68, P = 0.02 \); 20–40 min: group, \( F_{1.14} = 7.98, P = 0.01 \)). Locomotor activity decreased across the session in all rats, and there was no difference between groups during the final 20 min of testing (40–60 min: \( F_{1.14} = 2.78, P = 0.12 \)). In sum, HR-SE rats were initially hyperactive as compared to LR-SE rats when first exposed to a novel environment, and this difference declined over time as both groups of rats habituated to the environment, similar to previous reports (for example, Piazza et al., 1991).

**Blood corticosterone levels**

No significant differences were observed between corticosterone levels in HR-SE and LR-SE (HR-SE, 228.25 ± 50.43; LR-SE, 199.49 ± 21.96; group, \( F_{1.27} = 2.58, P = 0.12 \)). Therefore, the increased motor impulsivity observed in the HR rats following the SE was probably not due to heightened levels of corticosterone during the enrichment period, potentially ruling out the possibility that HR-SE rats found the SE more or less stressful than LR-SE animals.

**RT-qPCR results**

Compared to LR-SE rats, samples of the dHPC from HR-SE animals showed less mRNA expression for BDNF (Fig. 4; 

![Fig. 3. Locomotor activity in a novel environment, as measured prior to 5CSRTT task training, was greater in rats later designated as HR-SE. As compared to LR-SE animals, HR-SE rats exhibited greater ambulation in the novel environment in the first 40 min and in the total amount of activity recorded during the 60-min session. Values are presented as the average ± SEM. *P < 0.05.](image1)

![Fig. 4. Results from RT-qPCR analysis of dorsal hippocampus tissue, indicating significant decreases in mRNA encoding BDNF, the dopamine D1 receptor, and a trend decrease in the serotonin 5-HT\(_{2A}\) receptor in the HR-SE group. Data are presented as mean ± SEM. *P < 0.05, #P < 0.08.](image2)
impulsivity, but rather may be associated with a heightened locomotor response in a novel environment. The demonstration that environmental experience can directly elicit impulse control deficits in vulnerable individuals may capture the way in which certain contexts can exacerbate the dysregulation of impulse control. Although these findings have obvious relevance for substance dependence, such results also have implications for other psychiatric disorders in which context is a driving factor in symptom expression such as ADHD and even autism (Ashare & Hawk, 2012; Belin & Deroche-Gamonet, 2012; Ashburner et al., 2013). This laboratory-based model of context-induced impulsivity may therefore provide a novel way to investigate the neurobiology underlying such problematic disorders that has hitherto been lacking in the field.

Post-mortem analysis revealed that tissue samples from the dHPC of HR-SE rats contained lower levels of mRNA for the neurotrophic factor BDNF, as well as the D1 and 5-HT2A receptors. However, Western blot analysis did not confirm any differences in the expression of these proteins. Although CREB and pCREB were unaltered in the dHPC, a small decrease in pCREB was observed in the NAC of HR-SE rats in keeping with previous reports that CREB activity in this region can be reduced by exposure to an enriched environment (Green et al., 2010). These exploratory results demonstrate that modulation of neurobiological mechanisms within the dHPC and NAC may contribute to increased motor impulsivity following interactions with an SE.

### Discussion

Here we show for the first time that repeated interactions with a novel and SE can increase motor impulsivity in some individuals. For these environmentally-sensitive animals (termed high-responders to a stimulating environment, HR-SE), premature responses continued to increase over the 16 days of exposure to the SE, potentially indicative of a sensitised response. Interestingly, this change in behaviour during the SE challenge was specific to premature responses; accuracy, latencies, omissions and trials completed did not change from baseline levels. Post hoc analyses suggest that sensitivity to the SE could not be predicted by basal levels of impulsivity, but rather may be associated with a heightened locomotor response in a novel environment. The demonstration that environmental experience can directly elicit impulse control deficits in vulnerable individuals may capture the way in which certain contexts can exacerbate the dysregulation of impulse control. Although these findings have obvious relevance for substance dependence, such results also have implications for other psychiatric disorders in which context is a driving factor in symptom expression such as ADHD and even autism (Ashare & Hawk, 2012; Belin & Deroche-Gamonet, 2012; Ashburner et al., 2013). This laboratory-based model of context-induced impulsivity may therefore provide a novel way to investigate the neurobiology underlying such problematic disorders that has hitherto been lacking in the field.

**Increased motor impulsivity and locomotor activity in HR-SE**

To our knowledge, this is the first report of a subchronic environmental manipulation directly altering levels of impulsive action in rats. Likewise, our results demonstrate that individuals differ significantly with respect to the impact such novel and SEs have on subsequent behaviour. Although we were unable to measure locomotor activity or specific interactions with the enriched cage during exposure to the SE, HR-SE rats were more active in a novel environment.

### Table 4. Relative changes in mRNA in HR-SE as compared to LR-SE rats

<table>
<thead>
<tr>
<th>Primer</th>
<th>Orbitofrontal cortex</th>
<th>Medial prefrontal cortex</th>
<th>Basolateral amygdala</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>LR</td>
<td>HR</td>
</tr>
<tr>
<td>CREB</td>
<td>1.03 ± 0.07</td>
<td>1.00 ± 0.03</td>
<td>0.91 ± 0.04</td>
</tr>
<tr>
<td>BDNF</td>
<td>0.99 ± 0.15</td>
<td>1.17 ± 0.59</td>
<td>1.03 ± 0.10</td>
</tr>
<tr>
<td>D1 receptor</td>
<td>0.83 ± 0.24</td>
<td>1.04 ± 0.11</td>
<td>0.87 ± 0.11</td>
</tr>
<tr>
<td>D2 receptor</td>
<td>1.03 ± 0.57</td>
<td>1.11 ± 0.21</td>
<td>0.78 ± 0.06</td>
</tr>
<tr>
<td>5-HT1A receptor</td>
<td>0.78 ± 0.09</td>
<td>1.03 ± 0.09</td>
<td>1.01 ± 0.06</td>
</tr>
<tr>
<td>5-HT2A receptor</td>
<td>0.96 ± 0.10</td>
<td>1.00 ± 0.03</td>
<td>1.00 ± 0.08</td>
</tr>
<tr>
<td>cFos</td>
<td>1.09 ± 0.25</td>
<td>1.77 ± 0.77</td>
<td>0.89 ± 0.06</td>
</tr>
<tr>
<td>Arc</td>
<td>1.01 ± 0.25</td>
<td>1.65 ± 0.64</td>
<td>1.07 ± 0.08</td>
</tr>
<tr>
<td>CRF1</td>
<td>1.16 ± 0.18</td>
<td>1.25 ± 0.36</td>
<td>1.00 ± 0.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primer</th>
<th>Nucleus accumbens</th>
<th>Striatum</th>
<th>Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREB</td>
<td>i.s.</td>
<td>0.93 ± 0.05</td>
<td>1.04 ± 0.14</td>
</tr>
<tr>
<td>BDNF</td>
<td>0.62 ± 0.14</td>
<td>0.82 ± 0.12</td>
<td>1.70 ± 0.90</td>
</tr>
<tr>
<td>D1 receptor</td>
<td>0.95 ± 0.15</td>
<td>1.06 ± 0.15</td>
<td>0.83 ± 0.07</td>
</tr>
<tr>
<td>D2 receptor</td>
<td>i.s.</td>
<td>0.88 ± 0.10</td>
<td>1.04 ± 0.14</td>
</tr>
<tr>
<td>5-HT1A receptor</td>
<td>0.76 ± 0.34</td>
<td>1.41 ± 0.39</td>
<td>0.49 ± 0.16</td>
</tr>
<tr>
<td>5-HT2A receptor</td>
<td>0.88 ± 0.08</td>
<td>1.05 ± 0.15</td>
<td>0.75 ± 0.07</td>
</tr>
<tr>
<td>cFos</td>
<td>1.11 ± 0.12</td>
<td>1.06 ± 0.14</td>
<td>1.06 ± 0.10</td>
</tr>
<tr>
<td>Arc</td>
<td>i.s.</td>
<td>1.16 ± 0.07</td>
<td>1.03 ± 0.09</td>
</tr>
<tr>
<td>CRF1</td>
<td>i.s.</td>
<td>0.86 ± 0.07</td>
<td>1.03 ± 0.11</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard error of the mean. Bold values denote $P < 0.05$, $*P < 0.08$, i.s. denotes insufficient sample for analysis.
Table 5. Relative changes in protein expression

<table>
<thead>
<tr>
<th>Protein</th>
<th>Hippocampus</th>
<th>Nucleus accumbens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>LR</td>
</tr>
<tr>
<td>ERK</td>
<td>605.3 ± 39.6*</td>
<td>375.5 ± 40.4*</td>
</tr>
<tr>
<td>CREB</td>
<td>1.77 ± 0.33</td>
<td>3.80 ± 0.91</td>
</tr>
<tr>
<td>pCREB</td>
<td>59.3 ± 13.30</td>
<td>75.0 ± 8.52</td>
</tr>
<tr>
<td>BDNF</td>
<td>156 ± 28.30</td>
<td>113 ± 18.32</td>
</tr>
<tr>
<td>D1</td>
<td>14.4 ± 3.24</td>
<td>16.7 ± 2.33</td>
</tr>
<tr>
<td>5-HT2A receptor</td>
<td>1.68 ± 0.30</td>
<td>1.85 ± 0.24</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM. *P < 0.05, #P < 0.08. i.s., insufficient sample for analysis.

when first assessed at the outset of the experiment, prior to 5CSRTT training. Therefore, the higher levels of motor impulsivity observed in HR-SE rats following SE exposure may be related to increased activity in the SE, as the SE was designed to be essentially novel each day. However, it is important to note that elevated premature responding in HR-SE rats is not simply indicative of hyperactivity in the operant chamber, as might be expected following a period of increased exertion in a larger cage. Response latencies and omissions did not differ between HR-SE and LR-SE rats, indicating that these animals were not generally more active or motivated to perform the task. Instead, SE exposure selectively impairs animals’ ability to wait for a cue light to be illuminated prior to responding at the aperture array, a specific form of behavioural disinhibition (for review see Winstanley, 2011).

It could nevertheless be argued that HR-SE animals may have developed a greater preference for the reward following repeated SE exposure, which may then have contributed to behavioural disinhibition in anticipation of the reward-paired cue. Although this point is hard to address without further experimentation, previous work has shown that greater levels of premature responding are not necessarily accompanied by increased activation in anticipation of reward, or increased approach behaviour towards reward-paired stimuli, as measured by conditioned locomotor activity to food reward and sign-tracking respectively (Winstanley et al., 2004a). Hence, the behavioural expression of sensitivity to reward and reward-paired cues can be expressed independently from motor impulsivity, and are therefore thought to reflect at least partially distinct processes.

Previous reports failed to find any association between high levels of premature responding at baseline and locomotor activity in a novel or familiar arena, preference for a novel environment over a familiar one, or the time spent exploring a novel object (Loos et al., 2009; Molander et al., 2011). Hence, basal trait levels of motor impulsivity do not appear to be related to novelty reactivity or novelty-seeking. Our findings do not contradict this hypothesis: greater reactivity to the SE was not associated with basal levels of premature responding. However, the results presented here illustrate that exposure to an SE may unmask impulsive tendencies in subjects with a heightened sensitivity to novelty or stimulating situations, thereby demonstrating a novel synergy between motor impulsivity and sensitivity to novelty that could explain why these traits are often associated with similar clinical conditions.

Previous data indicate that a greater sensitivity to novelty measured by a one-time locomotor activity screen was predictive of enhanced amphetamine self-administration and greater levels of amphetamine-induced hyperlocomotion (Piazza et al., 1991). Given the relationship between heightened levels of motor impulsivity and cocaine self-administration (Dalley et al., 2007; Economidou et al., 2009), together with the results from the present study, in particular that HR-SE rats were more active in a novel environment, it could be hypothesised that heightened novelty reactivity (or sensation-seeking) may influence the expression of impulsivity and increase the susceptibility to develop addiction or abuse drugs. However, locomotor results were limited to four HR-SE rats animals within the second cohort. Additional studies are required to confirm the link between ambulatory behaviour within a novel environment and context-induced increases in impulsive action.

Greater activity in the SE would probably increase the frequency of contact with the enriched features of the environment, perhaps leading to a different quality of environmental interaction. As such, HR-SE rats, like novelty-seeking humans, may have experienced more novel and/or exciting situations within the SE. Whether such stimulation was deliberately sought out by the HR-SE rats is difficult to determine in the present study, but future experiments using behavioural monitoring technology could aim to address whether individual animals are more active or engage in more ‘thrill-seeking’ behaviours within the SE.

An alternative hypothesis is that the HR-SE rats found the complex environment more stressful than LR-SE animals, and that the increased impulsivity subsequently observed resulted from a negative mood state somewhat akin to the more recently-identified construct of negative urgency. Hyperactivity in a novel environment has previously been associated with elevated corticosterone levels in rats, albeit after a single exposure (Piazza et al., 1991). As blood corticosterone was only analysed at the conclusion of the current study, we cannot determine whether exposure to the SE increased or decreased corticosterone levels compared to a pre-exposure baseline. However, circulating corticosterone levels did not differ between HR-SE and LR-SE rats following exposure to the SE, suggesting that activation of the stress response is not a major factor contributing to the resulting behavioural disinhibition that differentiates HR-SE rats. In support of this suggestion, previous data indicate that corticosterone levels in animals classified as high or low in trait motor impulsivity on the 5CSRTT do not differ following exposure to a novel environment (Molander et al., 2011). Additionally, intra-cerebroventricular infusion of CRF or a CRF1 receptor antagonist also does not influence premature responding on this task, further indicating that increased activation of stress hormones does not necessarily precipitate impulsive action (Ohmura et al., 2009).

Molecular mechanisms underlying SE-induced motor impulsivity

Our observation that NAC samples from HR-SE rats tended to contain less of the active (phosphorylated) form of CREB is potentially in keeping with a previous report that housing animals chronically in an enriched environment (EE) leads to decreased pCREB in the NAC (Green et al., 2010). Furthermore, Green and colleagues demonstrated that decreasing CREB activity, via targeted RNA interference directed against the CREB protein, resulted in a similar behavioural phenotype as that observed following chronic housing in an EE, including increased anxiety in some tests, as well as enhanced sucrose preference. However, blunting CREB accumbal signaling does not appear to affect locomotor activity in a novel environment (Pliakas et al., 2001; Barrot et al., 2002; Green et al., 2010). Given that hyperlocomotion and slower habituation to the activity chamber predicted high impulsivity following repeated exposure to the SE, it may therefore be unlikely that lower levels of...
CREB activity in the NAC was driving the HR-SE phenotype. Decreasing accumbal CREB function generally results in a pattern of behaviour associated with reduced, rather than increased, vulnerability to drug addiction (Choi et al., 2006; Han et al., 2011; Larson et al., 2011), an observation which further decreases the likelihood that this molecular marker is key in the manifestation of context-induced impulsivity.

Out of all the regions analysed in the current study, the only area in which changes in multiple protein and mRNA levels were detected was the dHPC, suggesting a potential role for this area in mediating the HR-SE phenotype. The involvement of the dHPC in context-induced impulsivity fits with the substantial literature implicating this region in the processing of drug-related contextual information (Raybuck & Lattal, 2014; Xie et al., 2014). However, recent data suggest that manipulations of the ventral hippocampus, and not the dHPC, can elevate motor impulsivity through interactions with the mPFC (Chudasama et al., 2012; Abela et al., 2013). Exposure to the SE may therefore recruit the dHPC into the circuit involved in regulating impulsivity, leading to the hypothesis that the neural basis underlying context-induced impulsivity may be at least partly distinct from that implicated in basal impulse control. Although speculative, this suggestion is certainly not without precedent; sizeable literatures exist documenting neurobiological dissociations between context- vs cue-dependent forms of the same behaviour (e.g. fear-conditioning, Wang et al., 2013a; drug-seeking, Lasseter et al., 2010; Komorowski et al., 2013).

With respect to the specific findings linking the HR-SE phenotype to the dHPC, lower levels of DA D_1 and 5-HT_2A receptor mRNA were detected within this region in samples from HR-SE rats. DA has been heavily implicated in the locomotor response to a novel environment (Benigeri, 1983; Wang et al., 2013b). Furthermore, data from both animal and human subjects indicates that hypofunction at 5-HT_2A receptors increases motor impulsivity (Bjork et al., 2002; Higgin et al., 2003; Winstanley et al., 2004a,b; Jakubczyk et al., 2012). The novelty-seeking trait in humans has also been linked to the 5-HT transporter and 5-HT_2A receptor genes (Vormfelde et al., 2006; Suzuki et al., 2008; Salo et al., 2010). Similarly, levels of BDNF mRNA were lower in the dHPC of HR-SE rats. Given the well-established role for this neurotrophin in mediating cell survival and facilitating neurogenesis (Martinez-Levy & Cruz-Fuentes, 2014), this observation may be indicative of a decrease in neuroplasticity, a process that could affect numerous aspects of cognition.

Interestingly, exposure to the SE did not immediately influence premature responding and had no long-term consequences, as indicated by the lack of group differences following SE sessions. The physiological basis of this remains unknown. Chronic environmental enrichment has been found to alter dopamine-dependent processes involved in locomotor reactivity following amphetamine treatment (Bowling et al., 1993; Zhu et al., 2004). Furthermore, acute environmental enrichment (daily 2- to 4-h sessions) enhanced neurogenesis in the dentate gyrus of the hippocampus (Tyler & Allan, 2013). Similar, but transient, mechanisms within in the dHPC during repeated acute SE exposure in the present study may have led to structural changes involving the local dopaminergic, serotonergic and BDNF systems. These changes may have been ultimately expressed as an increase in premature responses in the HR-SE group during the final 4 days of SE. Upon removal of the SE, however, these mechanisms could have normalised along with level of premature responding. Further experiments are necessary to fully elucidate the neural processes involved in this apparently transient effect.

These changes in mRNA were not reflected in alterations in protein expression. Although this raises concerns over the functional significance of the mRNA changes, it is important to consider that the Western blotting technique used to detect protein levels is considerably less sensitive than the RT-qPCR method used to measure changes in mRNA, suggesting the analyses we used may have been unable to detect smaller yet biologically significant alterations in protein levels. There are also many molecular events between mRNA transcription and protein expression, including post-translational modifications and protein degradation (Vogel & Marcotte, 2012), that mean a one-to-one relationship between mRNA and protein levels is not always observed. In seeking to understand the pattern of results, we should also note that significant increases in ERK protein were reported in the dHPC of HR-SE rats. This protein is one of a family of mitogen-activated protein kinases essential for transferring signals from the cell surface to the nucleus, and is implicated in numerous signaling pathways that can be considered both upstream and downstream from changes in gene expression. Although ERK can trigger increases in gene expression, the end result of activating ERK can also be to inhibit the expression of certain genes, such as is observed here (See Wang et al., 2003). While the exact pathway remains unclear, the pattern of molecular changes isolated to the dHPC points to some role for this region in the differential response to the SE observed in HR-SE rats. It is also critical to note that, following multiple statistical analyses of these ex vivo data, the likelihood of type I error was increased, which may contribute to the robustness of these findings. Future experiments could test whether changes in the proteins flagged by this exploratory analysis are critical for the SE-induced increase in impulsivity, either through administering DA D_1 or 5-HT_2A antagonists directly into the dHPC or altering receptor protein expression via viral-mediated gene transfer.

Conclusion

These data provide a novel and compelling demonstration that exposure to an SE can trigger high levels of impulsivity in sensitive individuals, potentially through signalling within the dHPC, thereby providing a possible point of interaction between novelty-seeking or -reactivity and motor impulsivity with respect to addiction vulnerability. Modelling context-induced impulsivity in a laboratory setting can also provide a much-needed opportunity to study the mechanism by which high environmental load can lead to behavioural change. The idea that stimulation has both negative and positive effects on cognitive functioning dates back to the original demonstration that the relationship between arousal and performance is best described by an inverted-U-shaped function (Yerkes & Dodson, 1908). Numerous studies have demonstrated that personality factors such as extraversion and emotional stability impact subjects’ response to novel and challenging environments (see Nettle, 2006). This has wide-ranging consequences, from adaptive performance at work and success in romantic relationships to psychiatric vulnerability and resilience (e.g. Kendler & Myers, 2010; Tomroos et al., 2013; Huang et al., 2014). Understanding the neurobiological processes that determine how individuals differ in their reaction to challenging environments could therefore help to explain why certain contexts trigger maladaptive behaviours in susceptible individuals, and potentially lead to novel therapeutic interventions.

Acknowledgements

We thank Dr Stan B. Floresco for kindly allowing us to use the operant chambers in which locomotor activity was measured. This work was supported by operating grants awarded to C.A.W. from the National Sciences Foundation.
and Engineering Council of Canada (NSERC) and the Canadian Institutes for Health Research (CIHR). C.A.W. also receives salary support through the Michael Smith Foundation for Health Research, and C.A.W. and F.D.Z. both receive salary support from CIHR. C.A.W. has consulted for Shire on an unrelated matter. The authors have no other potential conflicts of interest, financial or otherwise, to disclose.

Abbreviations

5CSRTT, five-choice serial reaction-time task; 5-HT, 5-hydroxytryptamine receptor; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; cDNA, complementary DNA; CPu, caudate putamen; CREB, cAMP response element-binding protein; CRF, corticotropin releasing factor; CRF1, CRF 1 receptor; DA, dopamine; dHPC, dorsal hippocampus; ERK, extracellular signal-regulated kinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HR-SE, high responder to an SE; ITI, intertrial interval; LR-SE, low responder to an SE; mPFC, medial prefrontal cortex; mRNA, messenger ribonucleic acid; NAC, nucleus accumbens; OFC, orbitofrontal cortex; pCREB, phosphorylated CREB; Post-SE, five non-enriched 5CSRTT test days; RT-qPCR, real-time quantitative polymerase chain reaction; SE, stimulating environment.

References


