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ORIGINAL INVESTIGATION

Baseline prepulse inhibition expression predicts the propensity of developing sensitization to the motor stimulant effects of amphetamine in C57BL/6 mice

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Abstract
Rationale The startle reflex to a sudden intense acoustic pulse stimulus is attenuated if the pulse is shortly preceded by a weak prepulse stimulus. This represents a form of sensory gating, known as prepulse inhibition (PPI), observable across species. PPI is modulated by dopamine and readily disrupted by acute amphetamine. Prior repeated exposures to amphetamine also disrupt PPI even when the drug is not present during test, suggesting that a sensitized mesolimbic dopamine system—inducible even by a single exposure to amphetamine—might be responsible. However, this causative link has been challenged by inconsistent efficacy between different amphetamine pre-treatment regimes, which all robustly sensitize the behavioral response to amphetamine.
Methods Here, the presence of such a link in reverse was tested by comparing the propensity to develop amphetamine sensitization between high- and low-PPI expressing individuals identified within a homogeneous cohort of C57BL/6 mice. Comparison of dopamine content including its metabolites was performed separately in drug naïve mice by post-mortem HPLC.
Results Behavioral sensitization was substantially stronger in the low-PPI group compared with the high-PPI group, while the magnitude of their response to the first amphetamine challenge was similar. Dopamine content within the nucleus accumbens and medial prefrontal cortex was significantly higher in low-PPI relative to high-PPI mice.
Conclusion Individuals with weak sensory gating characterized by low basal PPI expression may be more susceptible to the development of dopamine sensitization and therefore at greater risk of developing schizophrenia. Conversely, high baseline expression might predict a resistance to dopaminergic sensitization.

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Introduction

Dopaminergic dysfunction remains a central pathophysiological theory of schizophrenia (Carlsson 1988; Howes and Kapur 2009; Howes et al. 2012). One theory suggests that the underlying hyperdopaminergia in schizophrenia is functionally similar to that of a sensitized dopaminergic state (Laruelle 2000). This can be induced in animals by prior exposure to psychostimulant drugs such as amphetamine or cocaine, which acts as an indirect dopamine receptor agonist (Pierce and Kalivas 1997; Robinson and Becker 1986). A single exposure to amphetamine is sufficient to substantially enhance the acute response to a subsequent drug challenge (Robinson and Becker 1986). The neuroplastic changes responsible for amphetamine sensitization have been studied using withdrawal models in the absence of any acute drug effect (Murphy et al. 2001; Peleg-Raibstein and Feldon 2008; Peleg-Raibstein et al. 2006a, b, c, 2008, 2009; Russig et al. 2005; for a review see Featherstone et al. 2007). Regarding the face validity of such amphetamine withdrawal models, one outstanding debate focuses on their reliability in capturing the sensorimotor gating deficits in schizophrenia (Featherstone et al. 2007; Peleg-Raibstein et al. 2006a; Russig et al. 2005) because such perceptual gating impairments are believed to yield sensory flooding and cognitive fragmentation that contribute to the psychotic experience and cognitive symptoms of schizophrenia (Braff and Geyer 1990; Swerdlow et al. 1994).

Sensorimotor gating in animals and human can be effectively assessed by the cross-species paradigm of prepulse inhibition (PPI) of the acoustic startle reflex (Braff et al. 1992, 2001; Swerdlow et al. 2001). PPI is demonstrated as the attenuation of the startle response to a sudden and intense startle-eliciting "pulse" stimulus when it is shortly preceded by a non-startling "prepulse" stimulus of considerably lower intensity. Perception of the prepulse is supposed to gate or inhibit the processing of the succeeding pulse stimulus, leading to a weaker response to the latter (Graham 1975). Deficiency in this fundamental form of sensory gating is frequently observed in schizophrenia patients (Braff et al. 1992, 2001), although it has also been reported in patients with obsessive-compulsive disorder, Parkinson's disease, and Huntington's disease (Abbruzzese and Berardelli 2003; Ahmari et al. 2012; Valls-Solé et al. 2004). Reports of similar deficiency in non-symptomatic relatives of schizophrenia patients further led to the suggestion that PPI deficiency represents an endophenotype of schizophrenia (Braff 2010). Healthy individuals in the general population scoring high on schizotypy personality scale are also associated with weaker PPI (Cadenhead et al. 2000).

Various experimentally induced PPI deficits have been considered as models of schizophrenia-related sensorimotor impairment (Geyer et al. 2001), but the expected link between amphetamine withdrawal and PPI deficiency seems to be critically dependent on the precise regimes of amphetamine exposures, even though they are all effective in potentiating the motor response to a subsequent amphetamine challenge (Murphy et al. 2001; Peleg-Raibstein et al. 2006a, b, c, 2008, 2009; Russig et al. 2005).

The present study undertook a fresh approach to examine this apparently elusive link. Instead of focusing on the hypothesized causal relationship between prior amphetamine exposures and subsequent sensorimotor gating deficiency, the present study evaluated whether individual differences in baseline sensorimotor gating function might predict the propensity to develop amphetamine sensitization. Subjects with low baseline levels of PPI were expected to be more vulnerable or responsive to the development of amphetamine sensitization, whereas subjects with high baseline PPI might even confer resistance. This experiment thus provides the first test of whether baseline PPI measures can predict an important form of dopaminergic plasticity central to schizophrenia pathophysiology. The outcome would be relevant to the possible use of PPI to identify individuals with higher risk for developing psychosis, and the contribution of environmental factors, such as stress, that are known to modulate the development of dopaminergic sensitization.

Here, a homogeneous cohort of naïve wild-type mice was screened by a standard PPI procedure to identify the upper (high-PPI) and lower (low-PPI) third individuals. To avoid the complication concerning different amphetamine withdrawal regimes, we employed the simplest procedure with a single amphetamine pre-exposure. The motor response to the first and second challenge of amphetamine (2.5 mg/kg, i.p.), separated by 5 days, was monitored in an open field. Post-mortem neurochemical analysis of dopamine and its metabolites in the brain was carried out in a separate cohort of mice having undergone a similar PPI screening. The high-PPI and low-PPI mice identified from this cohort all remained completely drug naïve until sacrifice. This further allowed us to examine if such divergence in baseline PPI might already be differentiated by markers for intrinsic dopaminergic functions.

Material and methods

Subjects

Two independent cohorts of 12-week-old male C57BL/6NCrl mice were used. They were bred in the Laboratory of Behavioural Neurobiology (Swiss Federal Institute of Technology Zurich) from C57BL/6NCrl (strain code 027)

breeding pairs originating from Charles River (Germany). The first cohort comprised 23 mice, out of which seven "high-PPI" and seven "low-PPI" subjects were identified. The second cohort comprised 100 mice, out of which the brains of 15 "high-PPI" and 13 "low-PPI" subjects were used in the post-mortem analysis of dopaminergic metabolites here. All mice were housed individually with ad libitum access to food and water, in a temperature- and humidity-controlled (22±1 °C, 55±5 %) vivarium maintained under a reversed 12/12 h light–dark cycle (lights on 1900–0700 h). All behavioral evaluations were conducted during the dark phase of the cycle. All procedures were conducted in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (1996) and had been approved by the Cantonal Veterinarian's Office of Zurich.

Prepulse inhibition of the acoustic startle reflex

Prepulse inhibition (PPI) of the acoustic startle reflex (ASR) was assessed using four identical acoustic startle chambers for mice (SR-LAB; San Diego Instruments, San Diego, CA, USA). Each chamber comprised a non-restrictive Plexiglas cylindrical enclosure attached horizontally on a mobile platform, which was in turn resting on a solid base inside a sound-attenuated isolation cubicle. A high-frequency loudspeaker mounted directly above the animal enclosure inside each cubicle produced a continuous background noise of 65 dB_A and the various acoustic stimuli in the form of white noise. Vibrations of the Plexiglas enclosure caused by the whole-body motion of the animal were converted into analogue signals by a piezoelectric unit attached to the platform. These signals were digitized and stored by a computer. In total, 130 consecutive readings were taken at 0.5-ms intervals (i.e., spanning across a 65-ms response window), starting at the onset of the startle stimulus in pulse-alone and prepulse-plus-pulse trials, and at the onset of the prepulse stimulus in prepulse-alone trials. The average amplitude over the 65-ms window was used to determine the stimulus reactivity. The sensitivity of the stabilimeter was calibrated daily to ensure consistency between chambers and across sessions.

The pulse stimulus employed was 120 dB_A in intensity and 40 ms in duration. Prepulses of various intensities were employed: 69, 73, 77, 81, and 85 dB_A, which corresponded to 4, 8, 12, 16, and 20 dB_A above background noise, respectively. The duration of prepulse stimuli was 20 ms. The stimulus onset asynchrony of the prepulse and pulse stimuli on prepulse-plus-pulse trials was 100 ms.

After being placed into the Plexiglas enclosure, the animals were acclimatized to the apparatus for 2 min before the first trial began. The 35-min-long test session began with six trials consisted of pulse-alone trials, which served to habituate and stabilize the animals' startle response. Subsequently, the animals were presented with 12 blocks of discrete test trials. Each block consisted of one trial of each of the following trial types: pulse-alone, prepulse-plus-pulse trials of each of the five levels of prepulse, prepulse-alone of each of the five levels of prepulse, and no stimulus (i.e., background noise alone). The session was concluded with the final set of six consecutive startle-alone trials. The interval between successive trials was variable with a mean of 15 s (ranging from 10 to 20 s). Four animals were tested at a time, and the apparatus was cleansed before the next four animals were tested.

The reduction of startle magnitude in prepulse-plus-pulse trials relative to those in pulse-alone trials constitutes PPI. Percentage PPI was computed as follow: [startle reactivity in the pulse alone trial−startle reactivity in the prepulse and pulse trial]/[startle reactivity in the pulse alone trial]×100 %.

Amphetamine sensitization and open field locomotor activity

The motor stimulant effect of amphetamine was assessed using eight identical open field arenas made of acrylic plastic, each measuring 40×40 cm in surface area and surrounded on all sides by a 30-cm-high wall. They were placed in the middle of two testing rooms, each housing four open fields, with diffused lighting (15 lx). The arenas were positioned directly under a digital camera transmitting images to a PC running the Ethovision tracking software (Noldus Technology, The Netherlands) at a rate of five frames per second. Locomotor activity was indexed by the cumulative displacement of the center of gravity of the subject's surface area over successive frames in successive 5-min bins.

The open field test consisted of three phases. First, the animals were gently placed in the center of an arena and left undisturbed for 15 min to measure baseline locomotor activity (baseline phase). Next, they were then injected with physiological saline (0.9 % NaCl) and returned to the arena for another 15 min (saline phase). Next, the animals were injected with amphetamine (2.5 mg/kg) and observed for 2 h in the same arena (amphetamine phase). Afterwards, they were returned to the home cage; the arenas were cleansed with 5 % ethanol and air-dried prior to testing of the next squad. All solutions for injection were freshly prepared on the day.

D-Amphetamine (in the form of D-amphetamine hemisulfate) was obtained from Sigma-Aldrich (Switzerland). Then 0.5 mg of D-amphetamine hemisulfate was dissolved in every milliliter of sterile physiological saline (0.9 % NaCl), and the solution was injected at a volume/body weight ratio of 5 ml/kg via the intraperitoneal route. All animals underwent two consecutive amphetamine challenge administrations separated by 5 days, when the animals remained undisturbed in their home cage. Behavioral sensitization to amphetamine was assessed within-subject by comparing the reaction to the drug in the two tests.

Segregation of high and low baseline PPI subjects

Based on their initial PPI screening results, the cohort of 23 mice were ranked according to their individual average %PPI values. Animals with the seven highest and the seven lowest mean %PPI scores were designated as "high-PPI" and "low-PPI" subjects, respectively, and were used in the amphetamine sensitization experiment. No further criteria of segregation were necessary as this did not yield any difference in startle reactivity as such (see full description in "Results" section below).

A separate cohort of mice (n=100) was used to generate "high-PPI" and "low-PPI" subjects as part of a large-scale study. The animals underwent the same PPI screening as described above. Four variables were calculated for each animal: (1) average reactivity in no-stimulus (background noise only) trials, (2) average reactivity in pulse-alone trials, (3) average percent PPI across all five prepulse-pulse conditions, and (4) the linear component of the downward sloping reactivity curve expressed as a function of prepulse intensity (+0, +4, +8, +12, +16, +20 decibel units above background) obtained by linear regression—the calculation was based on logarithmic-transformed (*ln*-transformed) reactivity scores.

Due to the larger size of the second cohort (N=100), we decided a priori that 5 % (the highest and lowest 2.5 %, i.e., in effect the three highest and lowest subjects) extreme subjects in any of the four critical variables should be excluded before compiling the "high-PPI" (N=23) and "low-PPI" (N=23) groups. This was carried out to avoid inclusion of subjects would conventionally be considered as outliers on statistical grounds and therefore not representative of the general population. Such trimming was considered less critical in the first cohort with a smaller sample size (N=23) because the top and bottom 2.5 % would only amount to 0.57 subject at each extreme.

Next, the remaining animals were ranked according to the two complementary PPI indexes (variables 3 and 4) and subjected to a median-split accordingly to each variable. Finally, only animals that received the same high–low classification by both variables were retained. This strategy of segregation ensured that the division was robust and minimized the potential distortion due to individual differences in baseline reactivity (pulse-alone reaction) rather than PPI expression (Csomor et al. 2006, 2008; Yee et al. 2005). The final outcome yielded 23 "high-PPI" subjects and 23 "low-PPI" subjects. Out of them, 15 and 13 subjects were randomly selected for the present post-mortem study.

Post-mortem neurochemistry

Levels of dopamine (DA) and its metabolites (dihydroxyphenylacetic acid, DOPAC; homovanillic acid, HVA) were determined using high performance liquid chromatography (HPLC) according to procedures established before (Peleg-Raibstein and Feldon 2006, 2008; Peleg-Raibstein et al. 2005; Bitanihirwe et al. 2010). High- and low-PPI subjects were killed and dissected in random order. The brains were extracted from the skull in toto within 1 min after decapitation and immediately frozen on dry ice and then were stored at −80 °C until dissection.

For dissection, the frozen brain was placed ventral side up on an ice-chilled plate covered with filter paper and was cut free-hand with an ultra-fine razor blade into in the coronal plane into approximately 0.5- to 1-mm coronal serial sections. Based on visible anatomical landmarks identifiable on the exposed coronal plane, five sections corresponding to the anterior–posterior levels: [+2.3 to +1.3], [+1.3 to +0.3], [−0.1 to −0.6], [−1.2 to −2.2], and [−2.8 to −3.8] mm relative to bregma, were selected by cross-reference with the Paxinos and Franklin's (2001) mouse brain atlas.

The chosen slices were collected and placed on an ice cold dissection plate for the removal of discrete brain regions, using a 1-mm micro-punch under visual guidance for the caudate putamen (CPu), medial prefrontal cortex (mPFC), nucleus accumbens (NAC), amygdala (AMY), dorsal hippocampus proper (dHPC), and ventral hippocampus proper (vHPC). Tissue punches from the left and right hemispheres of each brain area of interest were combined, weighed, and placed in 1.5-ml polypropylene microcentrifuge tubes containing ice-cold 300 μl 0.4 M $HClO_4$ and homogenized using ultrasound. After centrifugation at 10,000×g for 20 min at 4 °C, the clear supernatant layers were removed into a 1-ml syringe and filtered through a 0.2-μm nylon filter to separate the insoluble residue. This solution was immediately frozen and stored at −80 °C until injection onto the HPLC system. For all brain regions, with the exception of CPu and NAC, an aliquot of 50 μl was injected in the HPLC system. Due to the much higher concentration of dopamine in the CPu and NAC, only 20 μl was injected into the column.

Chromatographic conditions for detection of dopamine and metabolites

A HPLC system coupled with an amperometric electrochemical detector (Decade II; Antec, Leyden, The Netherlands) was used to determine concentrations of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA). The samples were injected via a refrigerated autoinjector (ASI-100; Dionex, CA, USA) equipped with a 100-μl injection loop. The samples were separated on a reversed-phase column (125 mm×3 mm YMC column, Nucleosil 120-3C 18; YMC Europe GmbH, Germany). An HPLC pump (P680; Dionex) connected to a pulse damper and a degasser was used to pump the mobile phase (see

below) throughout the system. The working potential of the electrochemical glassy carbon flow cell (VT-03; Antec, Leyden, Netherlands) was +0.70 V versus an ISAAC reference electrode. A chromatography workstation (Chromeleon; Dionex, Olten, Switzerland) was used for data acquisition and calculations. The mobile phase consisted of 250 ml of HPLC-grade acetonitrile, 5 l of aqueous solution containing 0.27 mM sodium ethylenediammoniumtetraacetate (disodium EDTA; $C_{10}H_{14}N_2O_8Na_2{\cdot}2H_2O$), 0.43 mM triethylamine $(C_2H_5)_3N$, 8 mM potassium chloride, and 0.925 mM octanesulfonic acid ($C_8H_{17}O_3SNa$) which acted as an ion pairing reagent. The pH was adjusted to 2.95 by adding concentrated phosphoric acid. This was pumped through the system at a flow rate of 0.4 ml/min. The position and height of the peaks of the endogenous components were compared with samples of external calibrating standard solutions. Detection limits were at least approximately 0.2 nM of transmitter or metabolite per sample (between 20 to 50 μl per sample—see above). This implies that readings roughly below three times the background noise levels would be considered as below the detection limit and dropped from data analyses to ensure detection reliability.

Statistical analysis

All data were analyzed by parametric analysis of variance (ANOVA) with the appropriate design, including the between-subject factor "baseline-PPI" corresponds to the contrast between "high-PPI" and "low-PPI" and necessary within-subjects factors (blocks, prepulse intensity, 5-min bins, and amphetamine challenges). To better conform to the normality and homoscedasticity assumptions of ANOVA, logarithmic transformation (indicated as "*ln*-transformed" in the text and figures) was applied to individual average reactivity data in the prepulse inhibition experiment [ln_e (reactivity score+e)−1] (see Csomor et al. 2008). A statistical significance of p <0.05 was used. Effect size was indexed by η_p^2. Data are presented as means±standard error of the mean (SEM) in all figures. The analyses were performed by SPSS version 18 (Chicago, IL, USA) running on a Microsoft Windows 7™ operating system.

Results

Segregation of baseline PPI performance prior to amphetamine treatment

The statistical outcomes of the respective ANOVAs in support of the successful segregation of high- and low-PPI groups are summarized in the table accompanying Fig. 1. As expected, the separation of "high-PPI" and "low-PPI" individual (n=7 each) led to the predictable difference in %PPI (Fig. 1a). The presence of a prepulse stimulus shortly preceding the startle-eliciting pulse stimulus was effective in reducing the startle response to the pulse stimulus in both groups, but this PPI effect was stronger in the high-PPI groups (see Fig. 1b). The two groups did not differ significantly in startle reactivity in trials which only the pulse stimulus was presented (i.e., pulse-alone trials). No difference in startle habituation was evident when the first and last blocks of six pulse-alone trials were compared (Fig. 1d), which is consistent with our previous studies in C57BL/6 male mice (e.g., Bitanihirwe et al. 2011; Singer et al. 2009; Singer and Yee 2012). The two groups, however, differed significantly in their spontaneous activity recorded in "no-stimulus" trials, which was stronger in the low-PPI group (2.76±0.19) than the high-PPI group (2.16±0.19). When we controlled for this non-specific difference, a clear group difference emerged between high- and low-PPI subjects in their direct reaction to the prepulse stimuli—defined as reactivity above that recorded in "no-stimulus" trials (Fig. 1c). The outcome is consistent with previous studies showing that PPI magnitude correlates with prepulse-elicited reaction in C57BL/6 mice (Yee et al. 2004a, b; Yee and Feldon 2009).

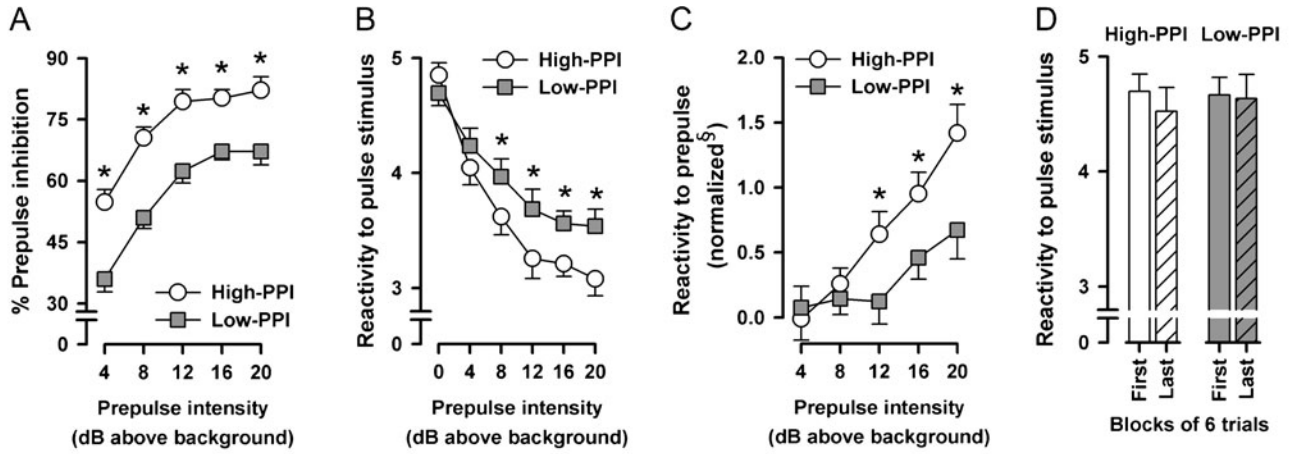
Differential acute and sensitized response to amphetamine between high- and low-PPI subjects

The three phases of the open field test of locomotor activity —pre-injection baseline, saline, and amphetamine phases— were separately analyzed.

Baseline phase Locomotor activity never differed between high- and low-PPI groups in this phase. Habituation across the two open field tests was evident, and within-session habituation was more clearly seen in the first than the second test (Fig. 2). A 2×2×3 (PPI baseline × tests × 5-min bins) revealed a significant effect of tests [$F(1,12)$= 135.20; p<0.0001; η_p^2=0.92], bins [$F(2,24)$=4.67; p<0.02; η_p^2=0.28], and their interaction [$F(2,24)$=5.04; p<0.02; η_p^2=0.30]. Neither the main effect of PPI performance nor its interactions achieved statistical significance.

The lack of a group difference in spontaneous open field locomotor activity stood in contrast to the presence of a baseline reactivity difference in the PPI experiment as recorded in "no-stimulus" trials (see above). This suggested that the two measures were likely unrelated. This is explicitly addressed by correlative analyses which revealed that while individual variation in baseline open field activity correlated significantly across the two tests [r=+0.64; p< 0.01; df=12], neither of these measures was significantly related to baseline reactivity in the PPI experiment [r=+0.14 to 0.02; p=0.64 to 0.94; df=12].

Saline phase Comparison of the saline phase between the two tests again revealed long-term habituation. Within-



Variables	ANOVA design		PPI baseline effect	Within-Ss factor effect	Interaction effect
Percent PPI	PPI baseline x Prepulse intensity	(2 x 5)	$F_{1,12}$ = 38.3, p <0.0001 η_p^2 = 0.76	$F_{4,48}$ =54.7, p <0.0001 η_p^2 = 0.82	F < 1 η_p^2 = 0.05
Reactivity in pulse-alone & prepulse-pulse trials	PPI baseline x Prepulse intensity	(2 x 6)	$F_{1,12}$ =2.18; p =0.17 η_p^2 = 0.15	$F_{5,60}$ =143.3; p <0.0001 η_p^2 = 0.92	$F_{5,60}$ =3.5; p <0.01 η_p^2 = 0.33
Reactivity in first and last blocks of pulse-alone trials	PPI baseline x Blocks	(2 x 2)	F < 1 η_p^2 = 0.003	F < 1 η_p^2 = 0.04	F < 1 η_p^2 = 0.02
Reactivity in "no-stimulus' trials	PPI baseline	one-way	$F_{1,12}$ =5.33; p<0.04 η_p^2 = 0.31		
Reactivity in prepulse-alone trials (normalized to "no-stimulus" trials)	PPI baseline x Prepulse intensity	(2 x 5)	$F_{1,12}$ =3.83; p =0.07 η_p^2 = 0.24	$F_{4,48}$ =19.80, p <0.0001 η_p^2 = 0.62	$F_{4,48}$ =3.38, p <0.02 η_p^2 = 0.22

Fig. 1 Summary of the segregation between high-PPI and low-PPI groups. Four sets of behavioral indices are presented here. **a** This graph depicts %PPI as a function of increasing prepulse intensity (as decibel units above background noise of 65 dB). Increasing prepulse intensity resulted in stronger inhibition of the startle response to the pulse, with the high-PPI mice consistently showing≈15 % more %PPI compared with the low-PPI mice. **b** This graph depicts the reactivity scores (*ln*-transformed) to the pulse stimulus in pulse-alone trials (i.e., prepulse intensity=0 dB above background) and prepulse-plus-pulse trials across increasing prepulse higher intensity. The successive reduction of the startle response with increasing prepulse intensity is indicative of the prepulse inhibition effect, which was more pronounced (i.e., steeper reduction) in the high-PPI group compared with the low-PPI group, leading to the significant group difference emerged from prepulse intensity of +8 decibel units or higher. **c** This graph illustrates the direct reaction (*ln*-transformed) to the prepulse stimulus with increasing intensity obtained in prepulse-alone trials. §: The reactivity score is normalized by subtraction from individual's baseline spontaneous reaction recorded in no-stimulus trials, and thus removing a significant confounding effect between groups (see tabulated ANOVA outcomes below). This is necessary for accurate evaluation at this lower range of reactivity, which indicated that prepulse-elicited direct response was also stronger in the high-PPI group relative to the low-PPI group from prepulse intensity of +12 decibel units onwards. **d** This *bar chart* compares the reaction to the pulse stimulus in the first and last block of trials, each comprising only six pulse-alone trials. The lack of a clear reduction from the first to the last block suggested habituation was weak or absent in both high-PPI and low-PPI groups. *Asterisks* (*) indicate significant between-group difference (p<0.05) revealed by pair-wise post hoc comparisons using the pooled variance of the overall ANOVA. The table below summarizes the design and outcomes of the five separate ANOVAs. Significant effects, including indexation of effect size by partial eta-squared (η_p^2), are highlighted by *black frames*. All data depicted refer to group means±SEM

session habituation was evident in low-PPI subjects in both tests, but it was only apparent in high-PPI subjects in the first session (Fig. 2). Instead of habituation, high-PPI subjects even exhibited a tendency of sensitization during the saline phase of the second test. It was also evident that low-PPI subjects responded to the saline injection more strongly than high-PPI subjects. These interpretations were supported by a 2×2×3 (PPI performance×open field×5-min bins) split-plot ANOVA of distance moved, which revealed a main effect of tests [$F(1,12)=66.88$; $p<0.0001$; $\eta_p^2=0.85$], bins [$F(2,24)=3.52$; $p<0.05$; $\eta_p^2=0.23$], tests by bins interaction [$F(2,24)=6.17$; $p<0.007$; $\eta_p^2=0.34$], and the three-way interaction [$F(2,24)=3.51$; $p<0.05$; $\eta_p^2=0.23$]. Post hoc pair-wise comparisons between high- and low-PPI subjects indicated that high-PPI subjects were more active than low-PPI subjects in the first and third bins of test 1, and the first two bins of tests 2.

Amphetamine phase Motor activity was potentiated by amphetamine, and this effect was stronger following the second injection, which constituted the behavioral sensitization effect. This effect was more pronounced in the low-PPI group

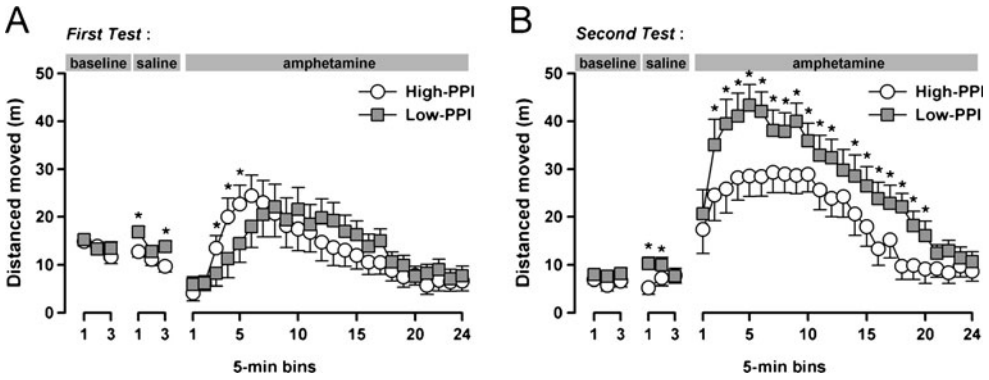


Fig. 2 The locomotor activity response to an amphetamine injection. **a** The locomotor activity levels in response to the first challenge of systemic amphetamine (2.5 mg/kg, i.p.) did not grossly differ between the high- and low-PPI groups. Their average as well as peak response was comparable, although the onset of the response appeared to be slower and more protracted in the low-PPI mice. **b** The response to the second challenge of amphetamine at the same dose yielded a stronger stimulation of locomotor activity compared to the first challenge, thus constituting the amphetamine sensitization effect. However, the low-PPI group now exhibited a consistently stronger response compared with the high-PPI group. Data presented are total distance moved (m) across successive 5-min bins (mean±SEM) in baseline (15 min), saline (15 min), and amphetamine (120 min) phases of the open field test. Sample sizes were seven per group. *Asterisk* (*) indicates significant group difference at p <0.05 based on post hoc comparisons using the pooled variance of the overall ANOVA

both in terms of the magnitude of the potentiated response and the rapidity of its onset (Fig. 2). In contrast, the behavioral sensitization effect though evident was relatively weak in the high-PPI group. Consistent with these interpretations, a 2×2×24 (PPI baseline×tests×5-min bins) split-plot ANOVA on distance moved yielded significant main effects of tests [$F(1,12)=34.80$; $p<0.0001$; $\eta_p^2=0.74$] and 5-min bins [$F(23,276)=32.11$; $p<0.0001$; $\eta_p^2=0.73$], and their interaction [$F(23,322)=3.32$; $p<0.001$; $\eta_p^2=0.39$]. The differential response between high- and low-PPI groups across the two tests was evident by the significant three-way interaction [$F(23,322)=1.75$; $p<0.05$; $\eta_p^2=0.18$] and the nearly significant PPI baseline by tests interaction [$F(1,12)=4.50$; $p=0.056$; $\eta_p^2=0.27$]. Post hoc pair-wise comparison between high- and low-PPI subjects suggested that high-PPI group showed a stronger response to the first amphetamine challenge at bins 3–5 following injection. On the other hand, low-PPI group showed a consistent elevated response to the second amphetamine challenge at bins 2 to 20 (except at the 13th bin).

In addition, we estimated the bin at which the peak activity response to amphetamine was recorded for each animal (Fig. 3). Behavioral sensitization in the form of a clear temporal facilitation was detected in the low-PPI group but not in the high-PPI group. A 2×2 (PPI baseline×tests) split-plot ANOVA of this variable yielded a highly significant interaction [$F(1,12)=18.68$; $p<0.002$; $\eta_p^2=0.61$], accompanied by a main effect of tests [$F(1,12)=8.5$; $p<0.02$; $\eta_p^2=0.41$]. Post hoc comparisons further revealed that low-PPI group was slower to reach peak response following the first amphetamine challenge but quicker in response to the second challenge [both p's<0.05], in agreement with the analysis based on distance moved (see Fig. 2).

Post-mortem neurochemistry

Among the brain areas examined, the high- and low-PPI groups were readily differentiated by all dopaminergic markers in the mPFC (Table 1). The mPFC DA levels of low-PPI mice were nearly 5-fold of that observed in high-

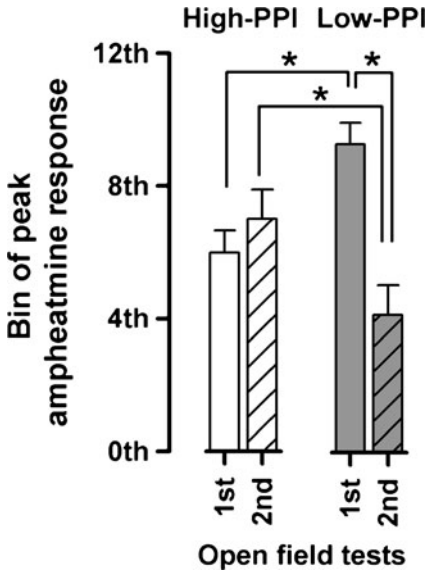


Fig. 3 Time to peak motor activity in response to amphetamine. The bin at which the peak activity score was achieved following amphetamine challenges (first versus second injection separated by 24 h) was calculated for each individual animal. While this measure hardly differentiated the first and second response to amphetamine for the high-PPI subjects, the behavioral sensitization observed in the low-PPI subjects was clearly associated with an earlier peak response. Data presented mean±SEM (N=7 per group). *Asterisk* (*) indicates significant group difference at p <0.05 based on post hoc comparisons using the pooled variance of the overall ANOVA

Table 1 Comparison of dopamine and its metabolites between high-PPI and low-PPI subjects of an independent cohort of never-drugged animals

Brain regions	DA			DOPAC			HVA			DOPAC/DA		HVA/DA	
	High-PPI		Low-PPI	High-PPI		Low-PPI	High-PPI		Low-PPI	High-PPI	Low-PPI	High-PPI	Low-PPI
mPFC	**0.07±0.05**	<	**0.34±0.05**	**0.17±0.05**	<	**0.64±0.05**	**0.13±0.02**	<	**0.25±0.02**	3.05±0.68	2.90±0.68	**2.59±0.04**	**1.11±0.04**
	η_p^2=0.43			**η_p^2=0.60**			**η_p^2=0.42**					**η_p^2=0.27**	
NAC	**3.55±0.49**	<	**5.46±0.51**	1.24±0.11		1.54±0.11	0.70±0.08		0.91±0.08	0.41±0.05	0.31±0.05	0.22±0.02	0.17±0.02
	η_p^2=0.22												
CPu	8.88±1.00		9.26±1.08	1.97±0.23		1.61±0.25	1.07±0.14		1.09±0.15	0.24±0.03	0.20±0.03	0.12±0.01	0.12±0.01
Amygdala	2.07±0.82		4.00±0.91	0.51±0.08		0.64±0.09	0.40±0.11		0.57±0.12	0.48±0.10	0.28±0.12	0.22±0.02	0.17±0.02
dHPC	1.08±0.51		1.45±0.51	0.26±0.08		0.34±0.08	0.19±0.06		0.26±0.06	1.09±0.26	0.59±0.26	0.79±0.23	0.28±0.23
vHPC	0.26±0.12		0.58±0.12	0.20±0.02		0.20±0.02	0.07±0.02		0.11±0.02	1.66±0.56	1.00±0.56	0.43±0.12	0.37±0.12

Dopamine (DA), dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) are expressed in nanograms per milligram of fresh tissue weight. The six brain regions included in the analysis were medial prefrontal cortex (mPFC), caudate putamen (CPu), nucleus accumbens (NAC), amygdala, dorsal hippocampus (dHPC), and ventral hippocampus (vHPC). Data presented are mean ± SEM. Detection limits were approximately 0.2 nM of neurotransmitter or metabolite per sample (20 to 50 μl per sample). After exclusion of subjects with readouts below detection limit, the final sample sizes were high-PPI group=10 to 15, low-PPI group=10 to 13, after exclusions of samples that were either below detection limits or considered as outliers for being more than three standard deviations away from the respective sample mean. Significant differences are indicated in bold type, with effect sizes indexed by η_p^2 and the direction of the group difference by ">" or "<"

PPI subjects [$F(1,24)=18.04$; $p<0.0005$; $\eta_p^2=0.43$]. This was accompanied by similar increases in dopamine metabolites: dihydroxyphenylacetic acid {DOPAC, nearly 4-fold [$F(1,24)=36.34$; $p<0.0001$; $\eta_p^2=0.60$]} and homovanillic acid {HVA, nearly 2-fold [$F(1,24)=17.30$; $p<0.0001$; $\eta_p^2=0.42$]}. The HVA/DA ratio in mPFC of low-PPI subjects was significantly lower than that of high-PPI subjects [$F(1,24)=8.82$; $p<0.01$; $\eta_p^2=0.27$], although the other metabolic ratio (DOPAC/DA) did not differ between groups.

Nucleus accumbens (NAC) DA levels were also significantly higher (+50 %) in the low-PPI mice relative to high-PPI mice [$F(1,25)=7.22$; $p<0.05$; $\eta_p^2=0.22$]. This difference was weaker in magnitude than in the mPFC and was not accompanied by any significant changes in DOPAC or HVA. As summarized in Table 1, no significant differences were detected in other brain regions.

Discussion

The present study tested the hypothesis that a random selection of adult male wild-type C57BL/6 mice stratified into high- and low-PPI performance groups might differ markedly in the development of behavioral sensitization in response to amphetamine in association with significant divergence in the dopamine system. It is conceptually linked to previous suggestions that baseline PPI could critically decide the magnitude and/or direction of response to antipsychotic drugs in healthy human volunteers (Csomor et al. 2008; Swerdlow et al. 2003; Vollenweider et al. 2006) and animal subjects (Hadamitzky et al. 2007). Here, we extended this important insight to mice by demonstrating that baseline PPI can also predict psychotomimetic drug action, importantly beyond PPI performance itself—namely, the sensitized motor response to amphetamine as well as selected dopaminergic markers confined to specific structures within the mesolimbic dopamine system. Thus, individual differences in sensorimotor gating as indexed by the cross-species PPI paradigm might provide useful insights into the functional state of the dopaminergic system, including its capacity for neuroadaptation implicated in the development of sensitization and, according to Laruelle's (2000) hypothesis, perhaps symptom genesis in schizophrenia.

Here, although the distinction between low- and high-PPI subjects was most readily distinguishable by their sensitized response to amphetamine, detectable divergence was already noticeable in their first acute response to amphetamine. Critical to the interpretation of the former is that the observed impacts of the low-high PPI segregation between the two occasions appeared opposite in direction (see Fig. 2). Thus, low-PPI subjects were somewhat less responsive to the first amphetamine challenge, yet they showed a substantially stronger response upon the second challenge

when compared to the high-PPI subjects. Hence, the latter cannot be considered as a scaling effect of the former. Conversely, the weaker sensitization effect seen in the high-PPI group cannot be merely attributed to a shift in the dose–response relationship relative to the initial amphetamine challenge.

Consistent with the known neural bases underlying the acute and sensitized response to amphetamine (Kauer and Malenka 2007; Pierce and Kalivas 1997), post-mortem quantification of dopamine and its metabolites in the drug naïve cohort revealed significant divergences primarily in the mesocorticolimbic dopamine system centering on dopamine-rich mPFC and NAC (see Table 1). The nigrostriatal dopamine measures taken from caudate putamen (CPu), in contrast, failed to differentiate between high- and low-PPI subjects. Notably, the overall neurochemical values obtained here are in general agreement with other similar studies in mice (e.g., Hadfield and Milio 1988, 1989), suggesting that the neurochemical divergences observed correspond well to deviations from the normal population means. One exception is the contrast between dorsal and ventral hippocampus dopamine content here. Statistical comparison revealed that dopamine content was significantly higher in the dorsal hippocampus [$F(1,23)=5.84$, $p=0.024$]. This is opposite to the gradient commonly associated with rats (e.g., Verney et al. 1985; Peleg-Raibstein et al. 2006a; Peleg-Raibstein and Feldon 2008), although we have obtained a similar, yet non-significant, trend before in C57BL/6 mice (Bitanihirwe et al. 2010). Hence, the possibility of a species difference might be likely, which may not be surprising given that a dorso-ventral gradient in hippocampal dopamine content is not consistent across rat strains (e.g., Rüedi-Bettschen et al. 2006). This highlights the importance of replicating our current findings in other species and strains.

The presumably pre-existing dopaminergic differences specific to the mPFC and NAC, however, did not translate into baseline difference in spontaneous locomotor activity. This is somewhat unexpected given that stimulation or blockade of dopamine transmission within nucleus accumbens affects spontaneous locomotor activity (e.g., see Ikemoto and Panksepp 1999), but it should be emphasized that no such extrinsic manipulations was employed here. Any neurochemical divergence revealed here between high-PPI and low-PPI subjects should not be interpreted as the equivalence of acute pharmacological blockade and stimulation of dopamine transmission in normal mice, respectively. The observed dopaminergic divergences here were not by design but emerged as correlates of an a priori behavioral segregation, so they cannot be equated with local manipulations. Indeed, evaluation of additional neural correlates in terms of brain neurochemistry, physiology, or anatomy is warranted in order to ascertain the full neurobiological significance of the segregation based on PPI performance.

Thus, the lack of a difference in spontaneous activity here does not contradict with available evidence that direct intervention of mesocorticolimbic dopamine targeting the NAC (Ikemoto and Panksepp 1999) or mPFC (e.g., Bast et al. 2002) can significantly modify spontaneous activity without a concomitant amphetamine challenge. One possibility is that a sustained shift of baseline dopaminergic differences over time might lead to functional compensation, e.g., a down-regulation of receptor density or sensitivity. The amphetamine sensitization regime effectively unmasked the functional relevance of the baseline dopaminergic divergence. Similar compensatory mechanisms might be responsible for the apparent lack of an effect on spontaneous activity by selective lesions of either mPFC or NAC until the animals were challenged by amphetamine (Lacroix et al. 2000; Tai et al. 1991; Yee 2000). Alternatively, dopamine tissue levels might be a poor correlate of synaptic dopamine transmission, and more direct measures of post-synaptic activation might not yield a difference in the absence of amphetamine challenge.

In this respect, it is worth noting that the first evidence of divergent activity levels emerged in response to the saline injection in the two open field tests. Despite a decrease in overall activity from the first to the second test, probably indicative of habituation to the open field, low-PPI but not high-PPI mice clearly showed an elevation in activity following saline injection, leading to a divergence in activity levels between them (see Fig. 2). Given that this was consistently observed on both test days, the behavior of the low-PPI mice is unlikely the result of conditioned response to the injection cues, which would only be expected to be possible in the second test.

This differential response to saline injection might reflect a stronger dopamine-mediated stress response in the low-PPI subjects, perhaps via mPFC connection to the hypothalamus (Vermetten and Bremner 2002; Weiss 2007). Hence, the regulation of locomotor activity by basal mesocorticolimbic dopamine system might indeed be more readily revealed when the system is activated or engaged by relevant external stimulus. Novelty or mild stress such as handling and injection is sufficient to stimulate dopamine efflux in the prefrontal cortex (Feenstra 2000; Feenstra et al. 2000; Peleg-Raibstein et al. 2005), which might be linked to the transient elevation of motor activation induced by the saline injection seen only in the low-PPI mice at the end of the habituation phase—an effect that was more akin to dishabituation rather than motor stimulation (to supra-normal levels) per se. However, it is perplexing as to why the same low-PPI mice did not exhibit at the same time a stronger reaction to the first acute dose of amphetamine. Instead, high-PPI mice were quicker in responding to the drug, though the magnitude of their reaction was not significantly stronger, considering the area under the curves during the amphetamine phase in Fig. 2a.

Sensitization is associated with PPI deficiency

The present finding is also in line with previous studies in healthy human subjects and in rats which reported that dopaminergic manipulations modify prepulse effects on startle magnitude in a manner that depends on basal levels of PPI (Depoortere et al. 1997; Swerdlow et al. 2003, 2006; Talledo et al. 2009), thus affecting only subjects with low PPI levels and with no effect on high-PPI subjects (e.g., Vollenweider et al. 2006; Hadamitzky et al. 2007). Reports that low levels of PPI in healthy subjects are correlated with psychosis proneness and schizotypy (e.g., Swerdlow et al. 1995) also indirectly suggest that subjects with low PPI might have a higher basal dopaminergic tone. The observation that the effects of amphetamine on PPI are inversely related to baseline levels of PPI is not unique. "Rate dependency" has been proposed as a possible mechanism underlying some of the therapeutic effects of stimulants in attention deficit hyperactivity disorder (Lyon and Robbins 1975). Thus, subjects with relatively high dopaminergic tone are disrupted behaviorally by amphetamine, while those with relatively low dopaminergic tone might have their performance enhanced.

PPI has been shown to be affected by treatments that alter dopaminergic transmission such as direct and indirect dopamine agonists; these effects can be blocked by administration of antipsychotic drugs (for review, see Geyer et al. 2001). There is some evidence that the effects of dopamine manipulations involve the nucleus accumbens and its associated neural circuits including afferents originating from the mPFC. Neurochemical analysis in the drug naïve cohort of high- and low-PPI mice revealed that segregation by baseline PPI performance also predicted a difference in intrinsic (i.e., not drug-induced) dopaminergic markers in the relevant brain regions. This raises the possibility that higher dopamine levels in the mPFC and nucleus accumbens predispose the development of sensitization to stimulant drugs. Further validation of such a link by in vivo microdialysis directly contrasting dopamine release during baseline and following amphetamine challenge in the same animals would be critical, and the present study points to the mPFC as the most promising target to be investigated first (cf., Yee 2000). Such in vivo within-subject studies would be necessary to delineate the neural substrates underlying the behavioral and neurochemical differences between low- and high-PPI subjects.

Conclusion: the predictive value of PPI

As the first psychopharmacological characterization of a behavioral segregation solely with respect to a single schizophrenia endophenotype (PPI expression) within a genetically homogeneous population inbred mice, we showed that PPI expression is sufficient to predict a specific form of dopamine plasticity—the sensitized motor response to amphetamine. This admittedly is based on a correlative approach, which is certainly insufficient by itself to support a causative link. Yet, our emphasis on a single mouse strain here suffered less confounding differences than models based on inter-strains comparison, such as that between DBA/2 and C57BL/6 mice (Flood et al. 2011; Singer et al. 2009), or the alternative approach of selective breeding pioneered by Hadamitzky et al. (2007), which produced separate rat lines with divergent PPI performance as heritable traits. In contrast, the use of inbred mice here minimizes genetic variation and emphasizes instead subtle environmental influences. These multiple lines of research all bear translational significance to human data demonstrating that basal PPI levels in healthy volunteers is also a critical determinant of their sensory gating response under the influence of antipsychotic drugs (e.g., Vollenweider et al. 2006; Csomor et al. 2008). Hence, PPI might serve as an effective screen for the early detection of individuals with increased environmental as well as genetic risks for psychotic proneness linked to dopamine sensitivity.

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