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Behavioural Brain Research 112 (2000) 13–22

BEHAVIOURAL BRAIN RESEARCH

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Research report

Behavioral and mesocorticolimbic dopamine responses to non aggressive social interactions depend on previous social experiences and on the opponent's sex

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Received 5 October 1999; received in revised form 28 January 2000; accepted 28 January 2000

Abstract

In these experiments we evaluated the relationship between behavioral and brain dopamine (DA) responses to social interactions. Subjects were group housed male mice confronted with a non aggressive male or female conspecific following either repeated defeat (defeated) or repeated non aggressive experiences (social). Defeated mice showed more defensive/submissive reactions then mice of the social group regardless of the opponent sex. However, mice defeated by females showed reduced social exploration without significant differences in non social exploration whilst the opposite was true for mice defeated by male opponents. Non aggressive social interactions enhanced dopamine metabolism in the prefrontal cortex (pFC) of DEFEATED mice regardless of opponent sex. However, only mice defeated by females showed enhanced dopamine metabolism and release in the nucleus accumbens septi (NAS) and olfactory tubercle (OT) following interaction with the non aggressive opponent. Finally, correlation between central and behavioral responses evidenced that 3,4-dihydroxiphenilacetic acid levels in the pFC were positively correlated with defensive behaviors and negatively correlated with non social exploration in mice confronted with male opponents but not in those confronted with females. The latter, showed a significant positive correlation between 3-methoxytyramine (3-MT) levels in the OT and defensive responses and significant negative correlation between social investigation and 3-MT levels in the OT and in the NAS. These results indicate a strict relationship between mesocorticolimbic dopamine transmission and behavior responses to social cues. Moreover, they strongly support the view that mesocorticolimbic DA modulates social behavior by affecting perceptive processing.

Keywords: Social behavior; Stress; Defense; Motivation; Learning; Fear

1. Introduction

A number of studies have indicated that brain dopamine (DA) systems play a crucial role in the modulation of social behavior of laboratory animals. For example, administration of direct as well as indirect DA agonists reduces social contact and dominance behavior whilst increasing defensive reactions in different species [22,23,29,38]. Moreover, mice treated with DA agonists exhibit defensive/submissive postures in the presence of non aggressive males, females, pups or their own reflection in a mirror ([31] for review). Finally, pro-defensive effects of pharmacological stimulation of brain DA receptors appear to be selective for social responses since behavioral effects of fear conditioning are reduced rather than enhanced by direct DA agonists [16].

Several lines of evidence indicate activation of DA transmission within the projecting fields of ventral teg-

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0166-4328/00/$ - see front matter
PII: S0166-4328(00)00157-1

mental (VTA) DA neurons by stimuli that promote expression of social defense in drug-free animals. Indeed, rats interacting with aggressive conspecifics exhibit greater increase of mesoaccumbens DA activity than rats interacting with non aggressive conspecifics [19] and defeat experiences promote activation of DA metabolism in mesocortical and mesolimbic areas of rats and mice [25,30]. Moreover, cues related to defeat experiences have been shown to activate mesocortical and mesoaccumbens DA release in previously defeated rodents [30,39].

Interestingly, mice previously defeated by an aggressive male conspecific show species-specific patterns of defensive/submissive behavior during subsequent social interactions. Such behavioral responses can be blocked by a DA antagonist [29]. These data suggest that social stimuli previously paired with defeat experiences enhance mesocorticolimbic DA transmission that, in turn, favors the expression of defensiveness in the presence of these stimuli.

However, enhanced DA metabolism and release in the nucleus accumbens (NAS) and prefrontal cortex (pFC), are also reported in animals exposed to non-social aversive experiences (see [4] for review) as well as to neutral stimuli paired with such experiences [13,34,41,46]. Thus, the relationship between expression of social defense and activation of mesocortical and mesolimbic DA systems remains to be explored. It has been suggested that the expression of fully integrated behavior, such as social behavior, involves neural mechanisms that can be separated into four stages of neural processing: sensory, perceptual, motivational and motor [24]. The relationship between activation of brain DA systems and social behavior is unlikely to be due to motor mediation but little is known about the other components [30,38,39].

In the following experiments, we investigated the relationship between brain DA and social behavior in mice exposed to different agonistic experiences. Thus, brain DA metabolism and behavioral output were analyzed in male mice confronted with non aggressive male or female conspecific following repeated defeat or non aggressive experiences in a classical intruder-resident paradigm.

2. Methods

All animals used in these experiments were NMRI outbred mice purchased from Plaisant (Rome, Italy) and kept in a 12-h light/dark cycle, at a temperature of 22 ± 1°C, given water and food ad libitum.

Experimental subjects were group housed (ten per cage: $26 \times 42 \times 15$ cm) male mice. Experimental procedure consisted of a pre-exposure and a test phase. During pre-exposure subjects were daily confronted with either defeat experiences (DEFEATED) or non aggressive social interactions (SOCIAL) in an intruder–resident paradigm for 3 consecutive days [7,18,29,30]. A total of four experimental groups ($n = 10$) were used. Groups were composed by mice daily exposed to (1) an aggressive female; (2) a non aggressive female; (3) an aggressive male; (4) a non aggressive male. On each pre-exposure day, intruders were exposed to an unknown mouse. On day 4, all subjects were introduced to a non aggressive opponent of the same sex of the residents they had been confronted with during pre-exposure (i.e. half of them with a female and half with a male) and let to interact for 5 min. In no case were intruders tested with individuals they had been confronted with before.

Aggressive males and lactating females were pair housed mice screened for attack behavior after delivery. The male and female of each pair were screened separately by introducing a male intruder into their home cage in presence of the litter. Animals showing similar attack latency and duration were used as aggressive residents. Non aggressive opponents were chosen for their lack of aggressive reactions toward the intruder. Because only a small percentage of resident males were reliably non aggressive, non aggressive male opponent were obtained by introducing a group-housed male mouse into a pair's home cage after the removal of both members of the pair but in the presence of the litter, 2 min before the experimental subjects. If one of both males displayed infanticidal tendencies, the test or pre-exposure session was interrupted and the infanticidal animal discarded.

In all cases, subjects pre-exposure began when the residents' pups were 5 days old (i.e. at the peak of maternal aggressiveness; see [26]). During the pre-exposure phase, non aggressive interactions lasted 3 min. Aggressive interactions were terminated when a cumulative attack time of 30 s was reached. Pre-exposure and tests were run in standard breeding cages ($33 \times 13 \times 14$ cm), in presence of the litter, during the second half of the light period in a sound-insulated cubicle illuminated by a 60-W lamp placed 2.4 m above the floor. The test session was videorecorded and successively reanalyzed for behavioral scoring. At the end of the 5-min test, all subjects were sacrificed by decapitation immediately upon removal from the test cage.

2.1. Behavioral categories

The frequencies of the following items of the intruder's behavior were recorded during the 5 min of test session (see [9], for a more detailed description).

2.1.1. Investigate

Olfactory exploration of the body of the other animal except the ano-genital region.

2.1.2. Ano-genital sniff

exploration of the ano-genital region of the other animal.

2.1.3. Sniff pups

Approach and investigation of the pups present in the test cage.

2.1.4. Evade

Retreating from the opponent.

2.1.5. Upright

The animal stands on its hind legs, normally presenting its ventral region to the other animal.

2.1.6. Sideways

The animal orientates itself broadside on to its opponent.

2.1.7. Self-groom

Washing the face with the licked fore paws or licking the forepart of the body and the tail.

2.1.8. Dig

Digging the cage bedding with the fore paws and kicking back with the hind paws.

2.1.9. Rear

Sniff of the air and cage walls by the animals standing on the hind paws.

2.1.10. Freeze

An additional behavior, 'Freeze': a crouched posture without visible movements of the body, was measured with the instantaneous sampling technique [21] and scored as the percentage of sample points (at 15-s intervals) in which the animal was immobile.

Behavioral data were transformed by using square-root transformations to meet assumptions of parametric tests [21]. Moreover, the 'defense' category grouping the defensive items sideways, upright and evade was also considered.

2.2. Biochemical analysis

Biochemical analyses were performed ex vivo on tissue samples. This approach was preferred to microdyalisis [48] for two main reasons. First, previous studies have shown that behavioral and central effects promoted by exposure to socially relevant stimuli in mice are extremely rapid, being significant within the first 5 min of exposure [29,30]. A very short time for a reliable analysis is allowed by this in vivo method. Second, ex vivo analyses allow investigation of the response of different brain systems in the same subject. Such an opportunity is certainly relevant for researches on the relationship between brain neurotransmission and complex behavior.

All subjects were sacrificed by decapitation followed by immediate head freezing. This method was preferred to microwave focusing since the latter procedure requires the animals to be restrained, a stressful procedure adding uncontrollable variables to the experiments [32]. Moreover, immediate head freezing allows one to obtain concentrations of 3-methoxytyramine (3-MT) comparable to or lower than those obtained by microwave irradiation [10,30,40,44] to be obtained and to reliably measure changes in the metabolite concentration following experimental treatment [3,30].

A number of studies have pointed to 3-MT in brain tissue as an index of DA release [5,2,17,42–45], while evidence has been presented to show that most of the 3,4-dihydroxypnelyacetic acid (DOPAC), and homovanillic acid (HVA) in the brain derives from a pool of DA that has never been released (Commissiong, 1985) [8,17,37,47].Therefore, high levels of acid metabolites accompanied by either increased or decreased 3-MT levels may depend on intracellular metabolism in monoaminergic as well as in non monoaminergic elements [8,37]. Finally, a strict parallel has been demonstrated between results obtained by this method and those obtained by intracerebral microdyalisis [32].

After decapitation the head was plunged directly into liquid nitrogen contained in a thermic box and left for 10 s. The frozen head was then stored at -10°C to allow it to reach a more manageable temperature before brain removal. The brain was then fixed vertically on the freeze plate of a freezing microtome. The freeze plate was used as a refrigerating table for punching, the temperature being maintained at -10°C. Punches were obtained from brain slices (frontal sections) no thicker than 300 μm. Stainless steel tubes of 0.8, 0.9, 1.0, 1.1, 1.5 and 2.3 mm inside diameter were used. Four brain areas were punced: frontal cortex (pFC), nucleus accumbens septi (NAS), olfactory tubercule (OT), hypothalamus (HYP). The co-ordinates were measured according to the atlas of [36] (coronal sections), as follows: pFC is two slices from section 95 to 140 (2.3-mm stainless steel tube); NAS is four slices from section 141 to 210 (1.1-mm stainless steel tube); OT is four slices from section 141 to 210 (0.8-mm tube); HYP is five slices from section 231 to 310 (0.9- and 1.1-mm tubes). The olfactory bulb (OB) was cut off at the level of section 55. The tissue samples were stored in liquid nitrogen until the day of the analysis.

DA, DOPAC, HVA and 3-MT were determined simultaneously utilizing a reverse phase high performance liquid chromatography (HPLC) procedure coupled with electrochemical detection [3,30,32]. 3-MT levels in pFC and HYP were not reported since this metabolite was undetectable with our analytical method in these brain areas. On the day of the analysis frozen

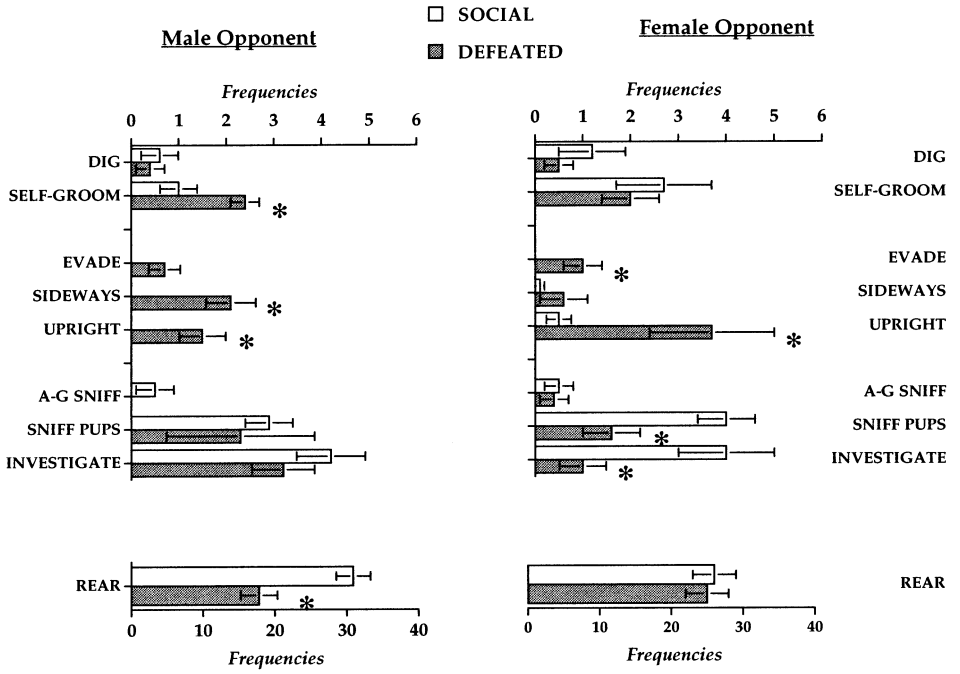

Fig. 1. Behavior (mean frequencies ± SEM) of male mice interacting with non aggressive conspecifics following either repeated non aggressive experiences (social) or repeated defeat (defeated). * $P < 0.01$ in comparison with social.

samples were weighed and homogenized in $HClO_4$ 0.1 N containing Na-metabisulphite 6 mM and EDTA 1 mM. The homogenates were centrifuged at 10 000 × *g* for 20 min at 4°C. Aliquots of the supernatant were transferred to the HPLC system. The HPLC system consisted of a Waters 460 electrochemical (EC) detector with a glass carbon working electrode and a pump (Waters 510). The potential was set at 800 mV (vs. Ag–AgCl reference electrode). The column, a Bondapak phenyl column (10-mm particle size 300 × 3.1-mm i.d.) was purchased from Waters Assoc. The flow rate was 1.1 ml/min. The mobile phase consisted of 4% methanol in 0.1 m Na–phosphate buffer pH 2.9, Na_2 EDTA 0.1 mM, and L-octane sulfonic acid Na salt (Aldrich); 0.5 mM 3,4-dihydroxyhydrocinnamic acid (Aldrich) was used as internal standard.

Raw data on DA and metabolites levels (ng/mg wet weight) were considered for statistical analyses. In the case of pFC results, also the DOPAC/DA ratios were considered since this measure has been frequently used to evaluate mesocortical DA response to aversive stimuli.

2.3. Statistical analyses

Statistical analyses were conducted with two-way ANOVAs (factors being: opponent sex, two levels, female and male; and experience, two levels, social, defeat). Whenever a significant main effect of defeat was attained, independent one-way ANOVAs were run for defeat effect. Correlations between behavioral and biochemical data were also considered in each sex group by Spearman's test. Due to loss of some tissue samples during dissection, degree of freedom for statistical analyses of biochemical data and correlation data are different from those reported for behavioral data.

3. Results

Behavioral data collected in the four experimental groups are shown in Figs. 1 and 2. A summary of statistical results for behavioral data is presented in Table 1. A significant overall effect of the opponent sex

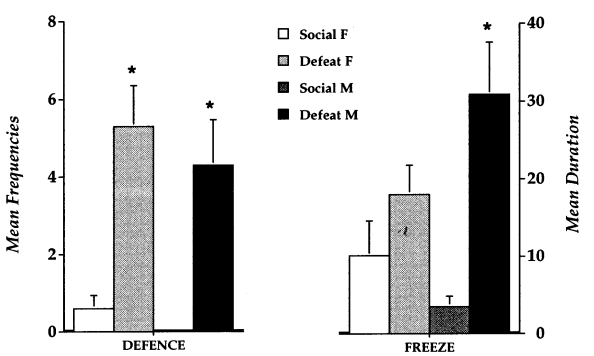

Fig. 2. Frequencies (mean ± SEM) of the behavioral category defense (sideways + upright + evade) and duration (mean ± SEM) of freeze in male mice interacting with non aggressive male (M) and female (F) conspecifics following either repeated non aggressive experiences (social) or repeated defeat (defeat). * $P < 0.01$ in comparison with social.

Table 1
Summary of statistics for behavioral data

Behavior	Opponent sex			Experience			Interaction		
	df	*F*	*P*	df	*F*	*P*	df	*F*	*P*
Investigate	1.36	1.35	ns	1.36	6.39	<0.05	1.36	1.35	ns
Sniff (ano-genital)	1.36	0.24	ns	1.36	1.32	ns	1.36	0.67	ns
Sniff pups	1.36	0.01	ns	1.36	21.02	<0.01	1.36	2.359	ns
Rear	1.36	0.29	ns	1.36	6.89	<0.05	1.36	4.35	<0.05
Dig	1.36	0.54	ns	1.36	0.9	ns	1.36	0.65	ns
Upright	1.36	5.24	<0.05	1.36	15.89	<0.001	1.36	2.07	ns
Sideways	1.36	3.66	ns	1.36	12.62	<0.01	1.36	4.78	<0.05
Evade	1.36	0.29	ns	1.36	9.25	<0.005	1.36	0.28	ns
Self-groom	1.36	0.79	ns	1.36	0.89	ns	1.36	2.66	ns
Defense (upright + sideways + evade)	1.36	0.98	ns	1.36	31.07	<0.001	1.36	0.06	ns
Freeze	1.36	0.49	ns	1.36	15.39	<0.001	1.36	4.69	<0.05

was found only for upright posture due to higher levels of this response in mice interacting with females. A significant increase of evade and upright and a significant decrease of investigate and sniff pups was observed in mice defeated by females. In defeated mice interacting with non aggressive males, a significant increase of sideways and upright and a significant decrease of rear was evident. As for defense category, it was increased in defeated mice regardless of the opponent's sex. Finally freeze was significantly increased only in mice previously defeated by male conspecifics.

Concentrations of DA and metabolites in the different brain areas of mice repeatedly exposed to non aggressive interactions are shown in Table 2. Effects of defeat are reported in Fig. 3 as percent changes from these concentrations. The summary of statistical results for biochemical data is reported in Table 3. An overall effect of the opponent's sex was revealed for DOPAC levels in the pFC, due to higher concentrations of this metabolite in mice interacting with females. A similar effect of the opponent sex was found for DOPAC/DA ratios (female opponent: 0.28 ± 0.03; male opponent: 0.23 ± 0.01). Defeated mice showed a significant increase of DOPAC in the pFC during social interactions regardless of the opponent's sex. However, only mice defeated by a female opponent showed a significant increase of DOPAC/DA ratio in this brain area on the test day. Higher concentrations of 3-MT and HVA were found in the NAS and OT of mice defeated by females whilst no effects were found in the HYP or OB.

Summaries of results from the analyses of correlation between behavioral items or categories and DOPAC and 3-MT levels or DOPAC/DA ratios are reported in Fig. 4. In mice interacting with females a significant positive correlation was found between 3-MT levels in OT and defense ($r(17) = 0.58$; $P < 0.01$) whilst social

Table 2
Basal levels of DA and metabolites in different brain areas of socially experienced mice[a]

	DA	DOPAC	HVA	3-MT
pFC				
Female opp.	246.6 ± 35.08	61.1 ± 2.00	141.1 ± 11.36	ND
Male opp.	244.4 ± 8.35	55.5 ± 1.75	154.4 ± 12.26	ND
NAS				
Female opp.	3843.7 ± 348.42	908.0 ± 32.06	996.6 ± 33.92	67.8 ± 2.59
Male opp.	3937.3 ± 166.11	904.8 ± 65.04	1018.3 ± 40.50	68.4 ± 2.61
OT				
Female opp.	7302.0 ± 119.61	566.2 ± 29.15	498.7 ± 45.13	67.5 ± 3.58
Male opp.	7345.7 ± 91.48	577.5 ± 20.33	506.2 ± 31.50	72.9 ± 2.86
OB				
Female opp.	317.0 ± 57.07	63.0 ± 8.38	76.2 ± 12.13	33.0 ± 4.52
Male opp.	298.5 ± 37.50	72.1 ± 9.05	92.1 ± 10.68	39.1 ± 4.38
HYP				
Female opp.	710.8 ± 80.80	310.0 ± 33.38	263.7 ± 34.37	ND
Male opp.	810.8 ± 111.69	292.5 ± 22.34	246.2 ± 15.22	ND

[a] Data are expressed as mean ng/g (wet weight) $\pm$ SEM. ND, not detectable.

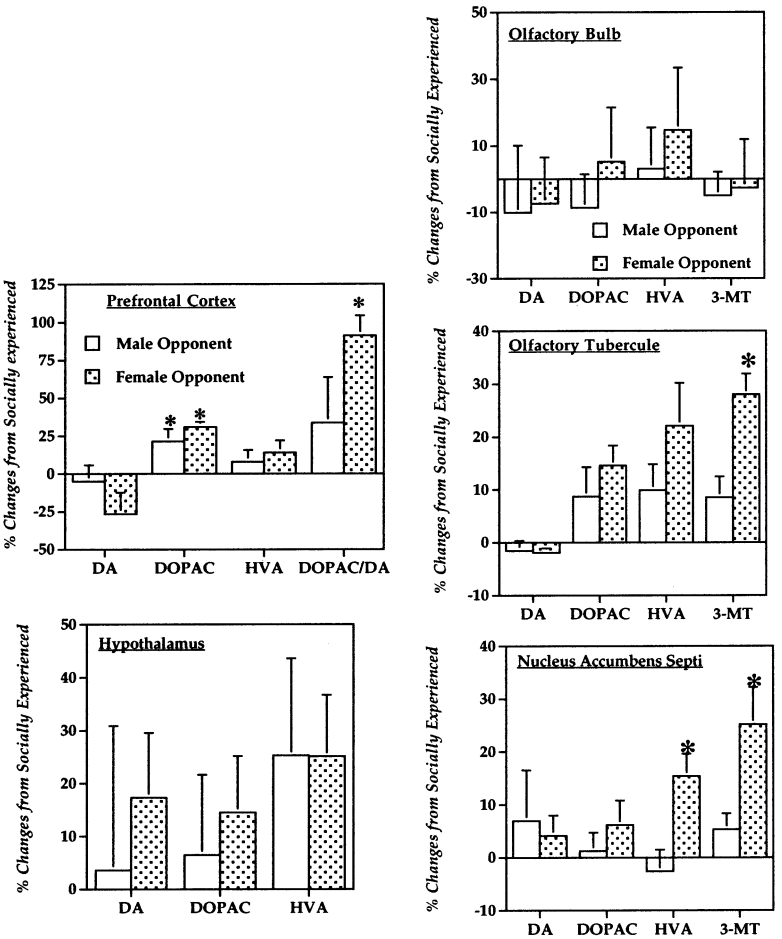

Fig. 3. Effects of interaction with non aggressive opponents on DA and DA metabolites levels of male mice repeatedly defeated by aggressive residents. Data are expressed as mean % changes from levels in mice with repeated experience of non aggressive interactions (socially experienced). Statistics were performed on raw data (see Section 2). * $P < 0.01$ in comparison with socially experienced.

exploration negatively correlated with 3-MT levels both in the NAS ($r(17) = 0.48$; $P < 0.01$) and in the OT ($r(17) = 0.48$; $P < 0.01$). No significant correlations were found between DOPAC levels or DOPAC/DA ratios in the pFC and behavior.

In mice interacting with males significant positive correlation were found between prefrontal DOPAC concentrations and defense ($r(17) = 0.54$; $P < 0.01$); or freeze ($r(17) = 0.64$; $P < 0.001$). A negative correlation was revealed between the DA metabolite and rear($r(17) = 0.51$; $P < 0.01$).

4. Discussion

The present results confirm previous data indicating that male mice defeated by aggressive males show high levels of species-specific defensive/submissive responses on subsequent encounters with non aggressive males [7,29]. Moreover, they extend this finding to behavior of mice defeated by females and interacting with non aggressive females.

However, other behavioral patterns exhibited by defeated mice depended on the opponent's sex. Thus, in the presence of a non aggressive male, previously defeated mice reduced to the minimum cage exploration spending most of the time in a freezing posture. Instead, mice defeated by females reduced social contact and avoided pups. These differences in the strategies acquired during the previous experiences with aggressive conspecifics might indicate that attack by male and female residents is elicited by different stimuli related to the intruder's behavior. Indeed, whilst territorial aggression by male residents may be provoked by environment exploration by the intruder, social and pups investigation may represent the stimuli that more reliably elicit the attacks by the lactating female because unknown sexually mature males may be infanticidal [27].

Moreover, the present results indicate that interaction with non aggressive conspecifics promotes activation of specific brain DA systems in previously defeated mice. Also in this case, some responses appear to be generalized whilst other are dependent on the oppo-

Table 3
Summary of statistics for DA metabolism in different brain areas

	Opponent sex			Experience			Interaction		
	df	*F*	*P*	df	*F*	*P*	df	*F*	*P*
PFC									
DA	1.31	0.90	ns	1.31	2.05	ns	1.31	1.06	ns
DOPAC	1.31	5.42	<0.05	1.31	15.83	<0.001	1.31	0.80	ns
HVA	1.31	0.71	ns	1.31	1.62	ns	1.31	0.001	ns
DOPAC/DA	1.31	7.01	<0.05	1.31	9.00	<0.01	1.31	2.87	ns
NAS									
DA	1.31	0.53	ns	1.31	1.09	ns	1.31	0.07	ns
DOPAC	1.31	0.28	ns	1.31	0.48	ns	1.31	0.27	ns
HVA	1.31	2.94	ns	1.31	2.54	ns	1.31	5.11	<0.05
3-MT	1.31	3.65	ns	1.31	10.55	<0.005	1.31	4.42	<0.05
OT									
DA	1.30	0.28	ns	1.30	1.44	ns	1.30	0.01	ns
DOPAC	1.30	0.13	ns	1.30	6.98	<0.05	1.30	0.65	ns
HVA	1.30	0.38	ns	1.30	4.42	<0.05	1.30	0.69	ns
3-MT	1.30	0.89	ns	1.30	17.39	<0.001	1.30	4.34	<0.05
OB									
DA	1.26	0.54	ns	1.26	0.9	ns	1.26	0.65	ns
DOPAC	1.26	0.20	ns	1.26	0.02	ns	1.26	0.24	ns
HVA	1.26	0.77	ns	1.26	0.29	ns	1.26	0.09	ns
3-MT	1.26	1.49	ns	1.26	0.09	ns	1.26	0.01	ns
Hyp									
DA	1.27	0.16	ns	1.27	0.34	ns	1.27	0.13	ns
DOPAC	1.27	0.83	ns	1.27	0.91	ns	1.27	0.15	ns
HVA	1.27	0.36	ns	1.27	3.96	ns	1.27	0.01	ns

nent's sex. Activation of mesocortical DA metabolism was observed in defeated mice in the presence of females or males, although the effect of previous defeat appeared to be more pronounced in animals confronted with females. Instead, only mice defeated by females showed increased DA metabolism and release in the NAS and TO when confronted with non aggressive opponents.

The effects of previous defeat experience on the mesocorticolimbic DA response to non aggressive interactions might be a conditioned stress response. In fact, activation of mesocorticolimbic DA systems is a well known stress response and a number of studies indicate conditioned increase of mesocortical and mesoaccumbens DA metabolism and release by cues previously paired with aversive experiences [13,41,46]. Moreover, converging evidence indicates that the number of DA systems being involved in stress response depends on the degree of severity of a stressful experience and that mild aversive experiences elicit a selective activation of mesocortical DA (see [4] for review). Thus, the selective activation of mesocortical DA metabolism in mice defeated by males might indicate that, for mice, the experience of being defeated by females represents a more severe stressor than being defeated by males. In line with this hypothesis, it has been suggested that the

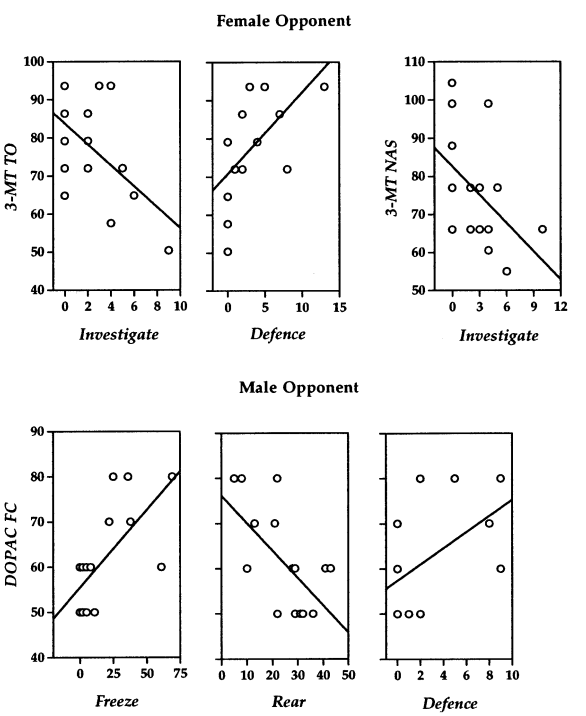

Fig. 4. Regression curves developed from significantly correlated behavioral and biochemical data.

aggressive pattern of lactating females differs from that of territorial males in being characterized by potentially lethal bites; i.e. bites aimed at intruder's vital organs [1].

However, it has been demonstrated that defeat by a male conspecific promotes enhanced DA metabolism and release in several brain areas besides pFC in rats and mice [25,30]. Consequently, the lack of mesolimbic DA response in mice defeated by males and subsequently exposed to non aggressive male opponents does not depend on the initial response to the defeat experience.

Enhanced DA release in the NAS of defeated rats or mice exposed to cues from an aggressive male conspecific behind a barrier has been demonstrated by ex vivo as well as in vivo methods [30,39]. The absence of similar effects in defeated mice interacting with a non aggressive male opponent might indicate the absence of conditioned cues on the test day. Indeed, a dominant aggressive animal may communicate its status to an intruder placed behind a barrier by a number of olfactory, behavioral and audible signals. Such signals would not characterize the non aggressive opponent used in these experiments whilst cues from a lactating female could be sufficient to elicit conditioned activation of mesolimbic DA in animals previously defeated by lactating females.

However, this explanation does not account for the behavioral and neurochemical effects of exposure to the non aggressive male. Indeed, defeated mice did show defensive reactions toward the non aggressive opponent and enhanced mesocortical DA metabolism in comparison with mice having experienced non aggressive encounters. These data indicate that defeated mice recognize potentially dangerous social stimuli in the test conditions. Consequently, the present results indicate that mesoaccumbens DA response in socially relevant contexts is cue-specific. The same holds true for OT because enhanced DA metabolism and release has been observed in this brain area following defeat by male dominants as well as following subsequent confrontation with cues from an aggressive male [30].

An alternative explanation of the observed differences in the central DA response observed in defeated mice, might be the different meaning of female and male opponents. Neuroendocrine studies have demonstrated that the severity of a given stressor does not depend on its physical impact but on psychological factors such as controllability, predictability, discrepancy and conflict [12]. A lactating female represents a potential mate, thus a potentially rewarding stimulus, for males. Defeat experiences add to this the discrepant information of a potentially dangerous, hence aversive, stimulus thus leading to conflict between opposing affective reactions toward the unknown female.

Different correlations between central and behavioral responses were found in mice interacting with females or males. Indeed, although both mesocortical DOPAC levels and defense were similarly increased by defeat experiences in mice interacting with males and females, these parameters were only correlated in mice interacting male conspecifics. Moreover, in these animals mesocortical DOPAC also correlated with freezing and, negatively, with non social exploration.

In mice defeated by females, defense positively correlated with TO 3-MT concentration and investigation was negatively correlated both with TO and NAS 3-MT levels. It should be pointed out that although mesoaccumbens DA release is enhanced by the presence of sexually relevant stimuli and positive incentives ([14] for review). However, NAS 3-MT levels were negatively correlated with social exploration suggesting a relationship with inhibition of preparatory behavior oriented toward the sexual goal. Hence, these results support the idea of a conflict-elicited response. Indeed, inhibition of appettitive responses is the classic output of conflict paradigms.

These results support the view of a strong relationship between behavioral and brain DA responses to socially relevant stimuli. Nevertheless they also indicate that brain DA does not mediate specific behavioral responses in social contexts. Instead, the strict dependence of correlation between central and behavioral responses on the opponent's sex suggests a role for mesocorticolimbic DA transmission in the fine tuning of complex behavioral patterns to socially relevant stimuli.

In conclusion, our results indicate that social interactions elicit specific patterns of behavioral and mesocorticolimbic DA responses that strongly depend on previous experiences and on social stimuli. Moreover, the strict interdependence between brain DA response, behavior and social cues observed in the present experiments, offers support to the hypothesis that DA might affect social behavior through an action on perceptual processing [6,38,39]. Such a possibility has major implications for clinical and preclinical research since disturbances in brain DA functioning might promote a distorted perception of social stimuli, causing inappropriate behavioral outputs [11]. To this regard, it should be pointed out that repeated administration of the indirect DA agonist cocaine, a prototypical animal model of psychostimulant-induced psychoses [20,28,33,35], promotes disturbances of mesocorticolimbic DA functioning [15] as well as altered behavioral responses to social stimuli [6].

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