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The rewarding efficacy of brain stimulation and its modulation by dopaminergic drugs in young adult and old BN F344F1 rats

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ABSTRACT

In old age there is evidence of waning motivation, and possibly lowering of mood. Physiologically there is a decline in the levels of brain neurotransmitters such as acetylcholine and dopamine, and loss of myelin. These changes might be expected to impair the functioning of brain circuitry for reinforcement, and to lead to impaired motivation. To evaluate the function of brain reinforcement mechanisms during aging we examined brain stimulation reward and its modulation by dopaminergic drugs in BN F344F1 rats aged from young adult (5 months) to old (37 months). Brain stimulation directly activates the neural circuitry for reinforcement, and the response rate–frequency tradeoff can be used to characterize the functioning of the system. Both young and old subjects readily learned to lever press for 0.6 s trains of 0.15 ms brain stimulation pulses, and there was no difference in the number of pulses per train required to maintain responding at 50% of the maximum rate (M50). Amphetamine (0.5 mg/kg) significantly reduced the M50, and the dopamine synthesis inhibitor alpha-methyl-*p*-tyrosine (100 mg/kg) increased the M50, but these effects were not influenced by the age of the subjects. The results suggest that in healthy animals dopaminergic modulation of reinforcement is functionally intact in old age.

1. Introduction

The popular belief that motivation and enjoyment of life decline in old age has received some support in surveys and suicide statistics (Gallo and Lebowitz, 1999; Prince et al., 1999), although it has also been pointed out that the majority of healthy elderly persons are not unhappy (Copeland et al., 1999). The burden of health problems and incipient dementia account for some of the problems of motivation and mood observed in the elderly, but there may also be specific changes in sensory and regulatory systems that contribute to waning motivation and mood (Mulligan and Moss 1991; Mowe et al., 1994; Sawka and Montain, 2000; Kenney and Chiu, 2001). Age-related changes in motivation are also observed in animals (Thunhorst and Johnson, 2003; Mattison et al., 2005).

Natural rewards such as food, water and sexual activity are not the only motivators that seem to diminish in importance as subjects age (Purifoy et al., 1992; Rolls et al., 1995; Ainslie et al., 2002). It is well known that consumption of rewarding drugs is strongly age dependent. Use of psychotropic drugs peaks in early adulthood, and then declines as the participants age (Gfroerer et al., 2003; US Department of Health and Human Services, 2004) although some continue drug use into old age (Dowling et al., 2008). Peak rates of use of marijuana occur at ages 14–16, and adults are unlikely to initiate use of this drug after 21 years of age (DeWit et al., 1997). Even among subjects who are so severely dependant on heroin that they come to the attention of the state, the number identified as still using declines with age (Winick, 1962; Vaillant, 1978; Price et al., 2001).

Many age-related deficits in motivation can be attributed to deterioration in exteroceptive and interoceptive sensory receptors. However, it is also possible that the brain circuitry of motivation may be impaired. This notion is consistent with the finding that drug self-administration declines with age, since drugs of abuse act directly on the neural substrate of motivation. In this regard, declining function in brain dopamine (DA) neurons may be significant, as DA is known to be involved in the reinforcing effects of brain stimulation reward (Franklin, 1978; Fouriezos and Wise, 1976; Lepore and Franklin, 1992), and of drugs of abuse such as amphetamine, cocaine and opioids (Spyraki et al., 1983; Wise, 1988; Fibiger et al., 1992).

DA has been found to be reduced in the cerebral cortex of old monkeys (Arnsten et al., 1994) and rodents (Lee et al., 2001). DA is also reduced in both ventral and dorsal striatum (Ponzio et al., 1982; Carfagna et al., 1985; Gozlan et al., 1990), though some studies failed to find such depletion (Godefroy et al., 1989). While levels of DA do not seem to be consistently reduced, other indices of dopaminergic neurotransmission are affected by age. In humans, the decrease of DA function in the striatum averages 6%–10% per decade, as indicated by PET and postmortem studies (Scherman et al., 1989). Age-related reductions in D2 receptor binding have also been found in the putamen and caudate of humans (Backman et al., 2000) and rodents

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(Han et al., 1989; Suzuki et al., 2001), and a number of studies have documented declines in the number of DA transporters (DAT) with age (Volkow et al., 1996; Moll et al., 2000; Haycock et al., 2003). The synthesis and turnover of DA is increased in substantia nigra (SN) tyrosine-hydroxylase-positive neurons following age-related loss of neurons (Greenwood et al., 1991). The potassium-evoked release of DA from striatal neurons has also been shown to diminish in old subjects (Friedemann and Gerhardt, 1992; Dobrev et al., 1995; Hebert and Gerhardt, 1998), and there is some evidence that aging may alter the way drugs of abuse interact with DA function. Alcohol-stimulated DA release in the nucleus accumbens is reduced in older rats (Yoshimoto et al., 1998), and amphetamine stimulated release may be reduced in old rats (Yurek et al., 1998).

Although anecdotal, behavioral and biochemical evidence suggests that the neural substrate for motivation might deteriorate in old age, there have been few studies on aging and the brain circuitry of motivation (Dowling et al., 2008). One of the most direct ways to examine the effect of aging on the neural substrate of motivation is through the brain stimulation reward (BSR) paradigm. BSR is believed to activate a system which mediates positive reinforcement or reward. There is evidence that the brain integrates the motivating effects of brain stimulation with natural motivation for food, water or sexual behaviour, and with the reinforcing effects of drugs of abuse (Gallistel and Beagley, 1971; Wise, 1987; Conover and Shizgal, 1994). The neural substrate of BSR includes the mesolimbic dopamine pathway from the VTA to the ventral striatum (Wise, 1987) and at least one population of caudally conducting neurons in the MFB which are moderately large myelinated fibres (Gallistel et al., 1981). This pathway could be particularly relevant to aging and motivation, because loss of myelin is one of the most significant changes in the brain with age (Peters, 2002).

Two studies have employed BSR to study motivational changes with age in rats. Lewis (1981) trained 6 month old male rats to lever press for hypothalamic stimulation, and then tested them periodically over the next 18 months. The self-stimulation response rate declined with age, but the decline could be reversed somewhat through the use of additional motivators, such as priming, increased stimulation intensities, retraining, and food deprivation. Although any one of these motivators alone was ineffective, combinations of motivators did increase responding. In addition, Lewis reported that a single injection of amphetamine (0.25 to 3 mg/kg) increased responding in the aged rats. However, the rate of responding does not discriminate between motivation and performance factors. More information can be obtained from the relationship between the response rate and the pulse frequency or intensity of a brain stimulation train. This measure can discriminate the effects of treatments on reward processes from their effects on performance (Gallistel and Freyd, 1987). Using a rate-independent, psychophysical method that measures threshold directly and has been shown to be independent of motor effects of a drug, Jha et al. reported BSR thresholds were lower in old rats, and that morphine decreased the threshold in young and old rats, except at the highest dose where morphine was less effective in old rats (Jha et al., 2004).

To date the influence of aging on the modulation of BSR by drugs that interact directly with the DA system has not been described. The aim of the present study was to determine if there are age-related changes in the sensitivity of the neural substrate for BSR, and whether the effect of dopaminergic drugs on this substrate changes with age. D-amphetamine and alpha-methyl-*p*-tyrosine were selected as dopaminergic drugs for the current study. Amphetamine (AMPH) increases release of DA and potentiates the rewarding effect of lateral hypothalamic brain stimulation (Hand and Franklin, 1983), while the catecholamine synthesis inhibitor alpha-methyl-*p*-tyrosine (α-MT) reduces brain dopamine and exacerbates the effect of natural dopamine deficiency (Birkmayer, 1969). It also decreases responding for rewarding brain stimulation (Poschel and Ninteman, 1971). As the focus was on normal aging, rats of the Brown Norway/Fischer 344 (F1) hybrid rat strain were selected as subjects.

2. Method

The experiments were reviewed by the Ethics Subcommittee of the McGill University Animal Care Committee and carried out in accordance with the guidelines of the Canadian Council on Animal Care.

2.1. Subjects

The subjects were 31 male Brown Norway/Fischer 344 hybrid rats obtained from the National Institute on Aging colony (Harlan Sprague–Dawley, Bethesda, MD). This strain tends to be free of serious diseases until very late in life, and no single disease process is solely responsible for deaths in these animals (Weindruch and Masoro, 1991).

At the time electrodes were implanted the age groups were 3 months (n=7), 8 months (n=5), 17 months (n=6), 23 months (n=5), and 35 months (n=7). Rats were housed individually in plastic cages, with free access to food and water. The colony room was maintained on a 12-h light/12-h dark cycle (lights off between 7 pm and 7 am). All experiments were conducted during the light part of the cycle.

2.2. Surgery

Under Domitor (1 mg/kg), Xylazine (20 mg/kg), and ketamine (100 mg/kg) anesthesia bipolar electrodes (Plastics One, Roanoke, VA) were implanted bilaterally, aimed at the lateral hypothalamus. Coordinates were: 2.8 mm posterior to bregma, 1.7 mm lateral to the midsagittal sinus, and 7.8 mm below the dura (Paxinos and Watson, 1998). The tips of the electrodes were separated and the bottom 0.5 mm of insulation was removed. Subjects were allowed to recover for a minimum of 3 days before training was instituted.

2.3. Apparatus

Single-lever operant boxes (dimensions 27.5 cm wide, by 28 cm deep, by 27.5 cm high) were used for all screening, training, and experiments. Boxes were constructed of clear Plexiglas, except for one wall which was of metal. A retractable lever (Coulbourn Instruments, Allentown, PA) was positioned in the middle of the metal wall, 6.5 cm above the metal rod floor. As the 35 month old rats had great difficulty moving around on the rod flooring, a plywood panel was placed over the rod floors during their sessions. The operant boxes were housed in individual sound- and light-attenuating chambers (65 cm×50 cm×52 cm), with a small house light (0.5 cm in diameter) positioned on the back wall of each box, 41 cm above the floor. A commutator (Plastics One, Roanoke, VA) mounted at the top of the operant chamber, connected the rat's leads to the stimulator output cable. Stimulation trains were 0.15 ms monophasic square-wave pulses, generated by electrically-isolated constant-current stimulators, which were driven by a computer-controlled, variable-frequency oscillator. To avoid the build-up of charge at the interface of brain and electrode, the electrodes were short circuited during the inter-pulse interval. Pulse frequencies and reinforcement schedules were set, and responses were recorded, by a Pentium II personal computer.

2.4. Procedure

2.4.1. Screening and training

Rats were screened for the presence of aversive effects or stimulation-induced motor effects, by delivering 600 ms trains of 0.15 ms pulses at a pulse frequency of 148 Hz, and amplitude of 200 μA. Rats that passed screening were placed in the operant box with one electrode attached to stimulating leads, given a few priming

trains, and then left alone to learn the lever-pressing response. On a subsequent session the process was repeated with the other electrode. During this time each lever press resulted in the delivery of one, 600 ms train at 148 Hz. Once the rat was spontaneously pressing the lever the pulse frequency was increased or decreased in an attempt to encourage robust responding. If necessary, the current intensity was also adjusted to lessen mild motor effects or aversive reactions. The electrode which yielded the most reliable responding in the initial training was used in all later phases of training and testing. Training on the FR-1 schedule continued until the rat was performing reliably. This usually took 1–3 sessions.

Once stable performance was achieved, rats were trained to press for stimulation of one electrode on an FR-2 schedule, then on an FR-5 schedule of reinforcement. Training in this phase also usually required 1–2 days of training on each schedule. Sessions were 45 min to 1 h in duration. On the next phase of training, rats were reinforced on a multiple schedule in which 3 min trials of random interval reinforcement (average interval 10 s) alternated with extinction (0 hz stimulation). An RI 10 s schedule ensured that the rat sampled the stimulation several times in a 3 min trial but the reinforcement density remained reasonably constant with fluctuations in the response rate. Trials were separated by a 10-s time-out, during which the lever was retracted into the wall of the operant chamber. Upon reintroduction of the lever at the start of each trial, a priming train was delivered to signal to the subject the stimulation that would be available during the trial. If a rat pressed two or more times during a trial where the pulse frequency was optimal, the next trial was an extinction (0 Hz) trial and extinction continued until the rat responded less than two times in a 3 min trial. When this criterion was met, the stimulation returned to the optimal frequency for the next trial, until the rat was again responding three or more times per trial. These conditions alternated throughout the 45–60 min session. This phase of training continued until responding declined rapidly during extinction trials and recommenced promptly at the start of a reinforced trail. This usually took 1–2 sessions.

2.4.2. Testing

Rate–frequency testing was similar to the last phase of training in terms of a 3-min trial structure, and time-out periods followed by a priming train. At the beginning of the session, the pulse frequency was set to the optimal frequency used during training. On subsequent 3 min trials, if more than 2 responses were recorded the pulse frequency decreased by 0.05 log units (to the nearest integer) until the rat emitted fewer than 2 responses in 3 min (extinction). On the next trial, immediately after extinction, stimulation was once again set to the optimal pulse frequency, and the cycle repeated. Sessions were 45–60 min, which usually resulted in more than one rate–frequency curve. Animals varied in the time taken to generate a curve, and only the first curve was at the same time relative to drug injection for all subjects. The first curve was therefore used for statistical analysis.

Rats were trained in this paradigm until the horizontal location of the rate–frequency curve on the frequency axis shifted by no more than 0.05 log units over two successive 4-session blocks. Once baseline frequency threshold was determined rats were tested with amphetamine (AMPH) injected 15 min before testing. Four injections of AMPH were given, each separated by one drug-free day of testing in the operant box. Thus, a minimum of 48 h separated each AMPH administration. Since illness and discomfort do not affect the locus of rise of the rate–frequency relation no injections were given on control days in order to reduce unnecessary discomfort for the subjects (Edmonds and Gallistel, 1977). Rate–frequency curves were averaged over 4 sessions, yielding one rate–frequency curve obtained under the influence of AMPH, and one rate–frequency curve for all 4 alternative drug-free test days.

When amphetamine testing was completed α-MT was tested. At least 4 drug-free test days separated AMPH and α-MT tests. Rats were given 100 mg/kg of α-MT 6 h before rate–frequency testing. Since old animals may be more sensitive and slow to recover from drug effects, a dose was selected to obtain adequate depletion of catecholamines while minimizing toxicity and catalepsy. At 50 mg/kg (4 h), α-MT blocks morphine-induced facilitation of self-stimulation but does not depress self-stimulation (Pert and Hulsebus, 1975). Above 150 mg/kg α-MT produces severe depression of self-stimulation and locomotor activity 4–8 h after injection (Stinus et al., 1972; Franklin and Herberg, 1974). We chose a dose of 100 mg/kg which is asymptotic for inhibition of tyrosine-hydroxylase (Widerlov et al., 1978), and has been found to elevate the threshold for self-stimulation 6–8 h after injection (Gibson et al., 1970).

2.5. Drugs

D-amphetamine sulphate (AMPH, Sigma-Aldrich, St. Louis, MO) was dissolved in saline, and administered subcutaneously at a concentration of 0.5 mg/kg (only this dose was used because pilot testing with 1.0 mg/kg produced too much stereotypy in this strain to obtain useable data). Alpha-methyl-*p*-tyrosine methyl ester (Sigma-Aldrich, St. Louis, MO) was dissolved in saline and administered IP. All rats were tested with both drugs.

2.6. Histology

Rats were killed under urethane anesthesia and the brain and head-cap were removed and stored in 10% formal saline for a minimum of 24 h, then sliced in 30 mm sections in a cryotome. Sections were stained with thionin and examined under a microscope to identify the site of the electrode tips with reference to Paxinos and Watson (1998).

2.7. Statistics

Results were analysed by SPSS 11.0 for Windows GLM with age groups (5) as a Between factor and treatments (doses or tests) as Within groups factors.

3. Results

3.1. Baseline performance

Rate–frequency curves were fitted to yield an estimate of the M50, the pulse frequency (in logarithmic units) at which the response rate was at half-maximal performance. Three curve fitting models (the Logistic, Weibull, and Gompertz) have been suggested for this purpose (Coulombe and Miliaressis, 1987) and they yield similar estimates of the M50. The Logistic model was selected because it produces reasonable estimates of M50 in cases where there are less than 4 data points on the steep portion of the curve.

Most of the rats in all age groups self-administered 0.6 s trains of brain stimulation at 200 uA, and there was no relationship between age and success. Only 2 rats failed to self-stimulate through either electrode (aged 3 months and 17 months). In a few cases, stimulation at 200 uA produced motoric and/or aversive effects, and in these cases the current was lowered, with one rat (3 months) receiving 150 uA trains, and 2 rats (17 and 23 months) receiving trains at 100 uA. At the end of training there was no difference between the age groups in terms of the pulse frequency required to support responding at half the maximum rate (M50).

It should be noted that the oldest age group of rats, (35 months) had swollen and possibly arthritic feet, and that they had difficulty moving about on the grid floor of the cage. For these subjects plywood panels were placed on the floor of the operant box during training and testing. No other special allowances were made for these rats.

3.2. Effects of amphetamine

Typical rate–frequency curves (RFC) for the baseline, amphetamine, and post-amphetamine drug-free sessions from 1 rat from each age group are shown in Fig. 1. It can be seen that the RFCs under amphetamine were left-shifted relative to both baseline and to post-drug, drug-free sessions, which did not differ from one another (F(4,19)=1.026, NS). The means and standard deviations of the averaged M50s for each age group and condition are shown in Table 1.

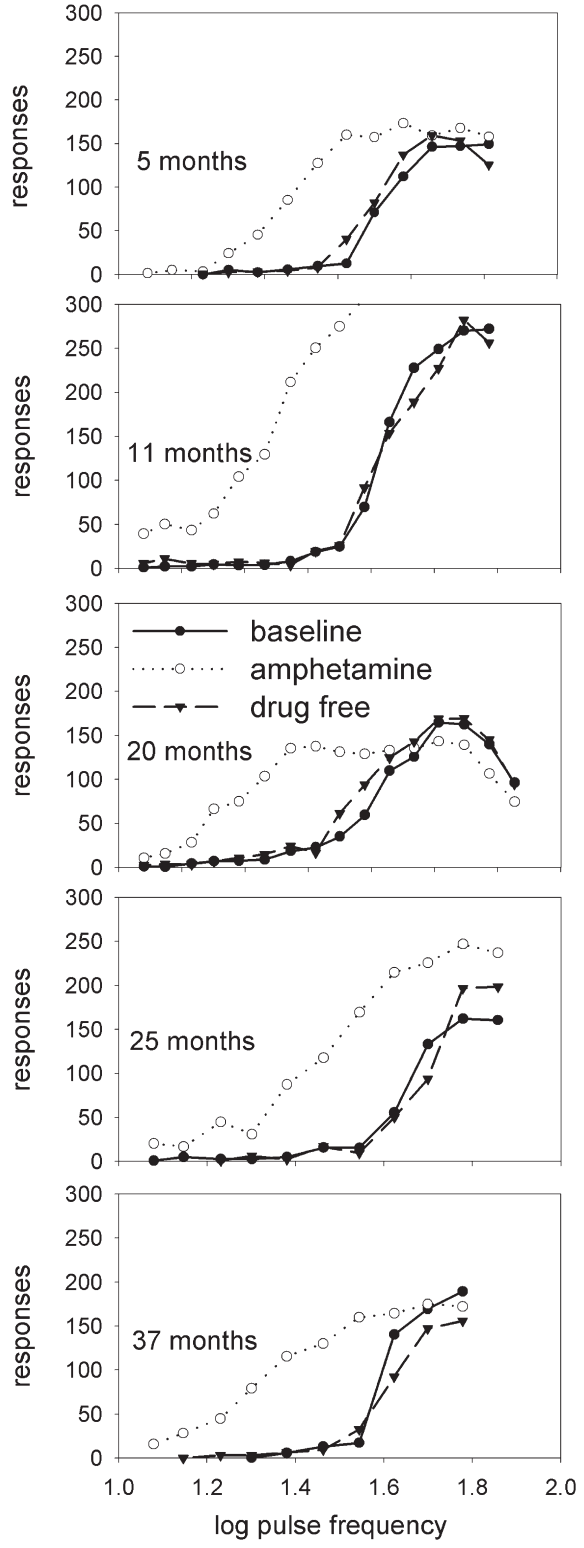

Fig. 1. Mean rate–frequency curves for BNF344 rats of different ages under baseline conditions, after amphetamine 0.5 mg/kg and drug-free post-amphetamine. Each panel shows rate–frequency curves of the rat closest to the median of its age group for the effect of amphetamine on the M50.

Table 1
Mean locus of rise (M50) for response rate–frequency curves determined drug-free, after 0.5 mg/kg D-amphetamine, or 24 h post-amphetamine in groups of BNF334F1 rats of different ages

Age in months	M50 of curve in drug-free state		M50 of curve under AMPH		M50 of curve on post-AMPH drug-free sessions	
	Mean	SD	Mean	SD	Mean	SD
5–6	1.782	.193	1.485	.241	1.773	.218
10–11	1.777	.168	1.430	.157	1.758	.168
19–20	1.754	.127	1.361	.165	1.728	.073
25–26	1.750	.232	1.427	.170	1.722	.223
37–38	1.576	.097	1.357	.208	1.581	.114

Data expressed as log pulses per train.

A 2-way repeated measures ANOVA confirmed there was no difference between age groups in the effect of amphetamine. Responding for BSR while under the influence of AMPH was enhanced (smaller M50), relative to responding for BSR on drug-free days (F (1,19)=311.193, $p<0.001$). There was no effect of age (F(4,19)=0.511, ns) and no interaction between age and amphetamine (F (4,19)=1.825, ns). A second ANOVA assessed whether or not the rats displayed post-amphetamine depression in responding for BSR, comparing M50s at baseline with performance on the drug-free test days that followed each of the 4 AMPH injections. No measurable after-effects of the AMPH were observed 24 h after injection (Drug: F (1,19)=3.056, ns, Age: F (4,19)=0.938, ns), and Drug by Age: F (4,19)=0.419, ns), indicating that no measurable after-effects of the AMPH were observed 24 h after injection.

3.3. Effects of alpha-methyl-p-tyrosine

Dopamine levels have been shown to decline as BSR sessions progress (Garris et al., 1999) so that the final descending sweep of an α-MT session might show a larger rightward shift than earlier RFCs. To examine this possibility, the position of the RFC in the session (either 'first' or 'last') was included as a factor along with Age and Drug treatment in a 3 way repeated measures ANOVA. The means and standard deviations of the averaged M50s for each age group and condition (first and last RFCs of the session) are shown in Table 2 and examples of RFCs are shown in Fig. 2.

ANOVA revealed a significant 3-way interaction (age × drug × sweep F (4,19)=3.294, p=.033). When drug effects on the first and last sweeps were analyzed separately, it was found that α-MT increased the M50 from both sweeps (F (1,19)=10.132 and 29.541 respectively, $p<0.005$) and there was no effect of age (F (4,19)=0.629 and 0.613,

Table 2
Mean locus of rise (M50) in log pulses per train for the first and last rate–frequency curves in a drug-free session and 6 h after 100 mg/kg α-methyl-p-tyrosine for groups of BNF334F1 rats of different ages

Age in months	M50 of curve in drug-free state, first RFC of the session		M50 of curve in drug-free state, last RFC of the session		M50 of curve in under α-MT, first RFC of the session		M50 of curve in under α-MT, last RFC of the session	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
5–6	1.774	0.211	1.780	0.241	1.821	0.162	2.024	0.443
10–11	1.788	0.238	1.838	0.218	1.823	0.132	1.973	0.217
19–20	1.792	0.140	1.700	0.146	1.915	0.122	2.023	0.143
25–26	1.732	0.193	1.695	0.199	1.743	0.160	1.881	0.211
37–38	1.626	0.035	1.712	0.201	1.782	0.192	1.727	0.047

Data expressed as log pulses per train.

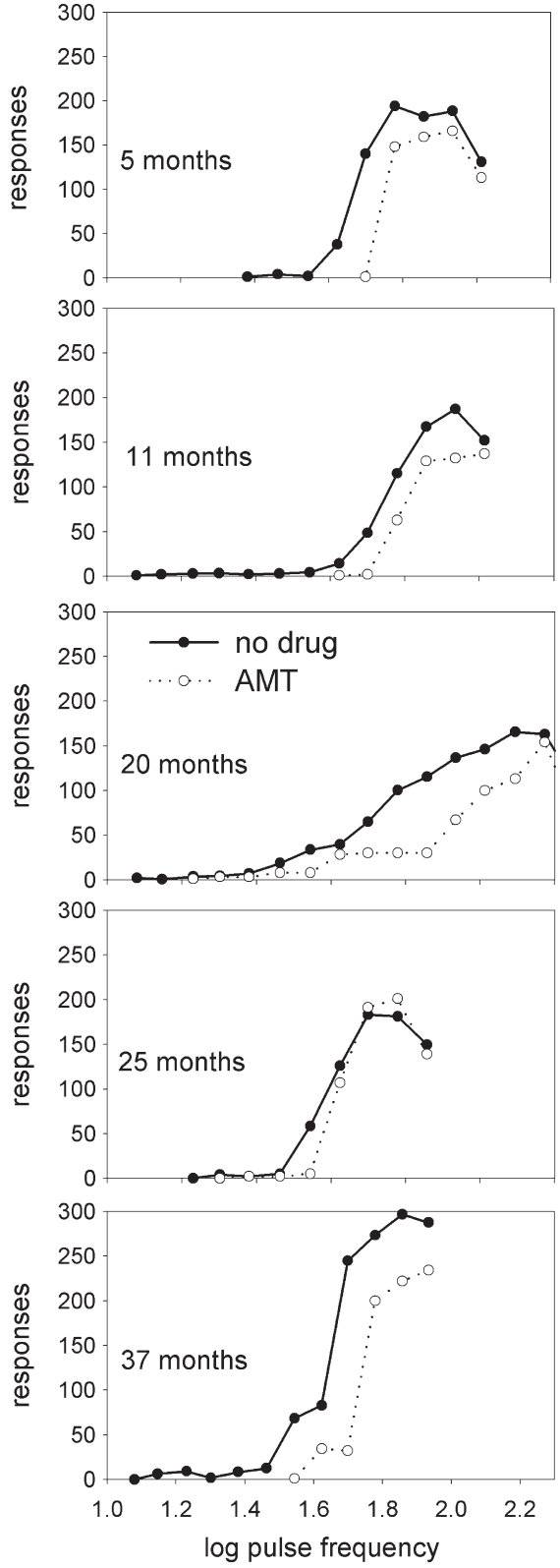

Fig. 2. Rate–frequency curves for BNF344 rats of different ages under baseline conditions, and 6 h after alpha-methyl-*p*-tyrosine 100 mg/kg. Each panel shows the rate–frequency curves of the rat closest to the median of its age group for the effect of alpha-methyl-*p*-tyrosine on the M50.

ns) or age×drug interaction (F (4,19)=1.329 and 2.279, ns). Examination of the within-session changes in RFCs showed that the shift after α-MT was greater on the last sweep than on the first sweep except for the oldest group (F (4,19)=3.295, p=0.033). It can be seen in Fig. 2 that not all subjects were affected by 100 mg/kg α-MT, but there were susceptible and resistant subjects in all age groups. To confirm that previous exposure to 4 injections of AMPH did not have any long-lasting changes on performance, responding during the baseline period prior to AMPH testing was compared to the baseline period prior to α-MT testing. No significant differences were found (Drug exposure: F (1,19)=0.085, ns, Age: F (4,19)=0.691, ns, Drug exposure by Age: F (4,19)=1.756, ns). Finally, to examine whether exposure to α-MT had any long-lasting changes on performance, performance during the baseline period prior to α-MT testing was compared to the performance 24 h after α-MT . No significant differences were found (Drug exposure: F (1,19)=0.085, ns, Age: F (4,19)=0.785, ns, Drug exposure by Age: F (4,19)=0.136, ns).

4. Discussion

Our results indicate that the functioning of the neural substrate of reward is preserved from young adulthood to old age. The first index of the reward system function was the range of frequencies required to maintain half-maximal performance. We tested rats ranging in age from 5 months to 37 months. Rats 6 months old are young adults, while by 36 months 50% of the population has died (Turturro et al., 1999). By comparison, 50% of the human population of the USA has died by approximately 75 years. Our oldest group of subjects was, therefore, truly old. Nevertheless, the range of pulse frequencies required to maintain performance did not differ between age groups. A pulse intensity of 200 mA was used for most subjects regardless of age, and the few exceptions were not in any one age group. The oldest group was readily able to acquire and maintain lever pressing for BSR, despite some difficulties in walking. Indeed, other studies have noted that while older rats show movement disorders such as foot dragging or hind limb paresis, this does not appear to interfere with learning (Spangler et al., 1994) or with performance (Tanila et al., 1994).

Old rats showed no deficits in the response to moderate doses of dopaminergic drugs. All rats displayed an enhancement of the rewarding effects of brain stimulation in response to 0.5 mg/kg AMPH, as shown by a leftward-shift of the RFC. The size of this shift averaged 0.3 log units, which represents a 50% increase in the reinforcement efficacy of the stimulation (Gallistel and Freyd, 1987). This is a sizable shift in comparison with earlier studies. Bossert and Franklin (2003) compared the performance of self-stimulating rats under AMPH and under vehicle. At 0.5 mg/kg of AMPH, the M50 was decreased by approximately 22% as compared to performance under vehicle, and doses of 1.0 and 2.0 mg/kg yielded shifts of approximately 36% and 40%, respectively. Gallistel and Freyd (1987) found that 0.5 mg/kg led to leftward shifts of 0.1 log unit, while 1 mg/kg yielded shifts of 0.2 log units. However, it should be noted that the studies used different rat strains — BN F344F1 (present study), Long–Evans (Bossert and Franklin, 2003) and 'albino' (Gallistel and Freyd, 1987). It is likely that rat strains are not equally sensitive to psychostimulant drugs. As noted above, 1.0 mg/kg AMPH produced stereotyped behaviour in preliminary tests indicating that the BN F344F1 strain is particularly sensitive to AMPH. Still, it is clear in the present study that AMPH exerted a powerful reward enhancing effect, and no significant effect of age was observed. In addition, no post-amphetamine depression was observed after AMPH injections.

To reduce dopamine availability, rats were given a dose of α-MT (100 mg/kg) that has been shown to produce a severe depression of brain catecholamines 4–6 h after injection (Dominic and Moore, 1969). All age groups showed a decline in the rewarding efficacy of BSR, as represented by a rightward shift in the RFCs, and this shift increased with the time spent responding under α-MT, except for the oldest group. The shift was only 0.07 log units when the RFCs of the first sweep of the α-MT and drug-free conditions were compared, but increased to 0.19 log units on the last sweep of the session. Given that shifts of 0.05 log units or more are considered behaviourally significant (Gallistel and Freyd, 1987), the shifts produced by α-MT

represent a substantial decrease in the rewarding effect of brain stimulation and this decrease was similar for all age groups. It should also be noted that "the doses of α-MT required to substantially reduce or abolish self-stimulation are close to the lethal dose"(Edmonds et al., 1974). Thus, while increasing the dose of α-MT might have led to larger effects, a significant loss of subjects may have occurred.

Though full dose–response relations would be necessary to show definitively that there are no differences in the drug responses of old and young rats, the moderate doses of amphetamine and α-MT that were tested here shifted the M50 over a range that averaged about 0.5 log units i.e. an approximately three fold shift in the frequency threshold. Within this range there were no differences between age groups. That old rats were not less sensitive to AMPH, or more sensitive to α-MT than young rats is surprising, in view of evidence that old rats have reduced DA and higher turnover of DA (Greenwood et al., 1991; Lee et al., 2001). One might predict that older rats with naturally depleted DA systems would be hypersensitive to drugs that inhibit DA synthesis (Breese et al., 1973). Indeed levels of extracellular DA, and amphetamine-evoked overflow of DA, have been reported to be reduced in older (18–19 and 24–25 mo) BN F344F1 rats, in parallel with reduced basal and amphetamine-induced motor activity (Yurek et al., 1998). Likewise, the locomotor stimulant effect of nomifensine was reduced in older rats, as was the potassium-evoked DA overflow in the striatum, measured by in vivo electrochemistry (Hebert and Gerhardt, 1998). However, others have found few changes with age. In young (6–8 month) or old (24–26 month) F344 rats D-amphetamine produced similar, dose-dependent increases in DA overflow measured by microdialysis (Purdom et al., 2003), while potassium stimulated DA release and its recovery were similar in young and old Wistar rats (Shui et al., 1998). Our results are consistent with the latter studies. Similar findings have been reported for the effects of opioids on BSR. Jha et al. examined the effects of morphine on BSR using a rate-independent method. They found that 24 month old rats had a lower BSR threshold than 6 month old rats, that morphine reduced the threshold in both groups, and there was no age×dose interaction (Jha et al., 2004).

In conclusion, the reward system and its modulation by dopaminergic drugs (this paper), or by opioids (Jha et al., 2004), does not seem to be impaired in rats as old as 37 months in comparison with young adult and middle aged rats.

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