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Effects of beta-adrenoceptor blockade on components of human decision-making

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Abstract *Rationale:* Converging evidence from studies with neurological patients and brain imaging studies with healthy volunteers suggests that the capacity to make choices between actions associated with probabilistic rewards and punishments depends upon a network of cortico-limbic systems including the orbitofrontal cortex, cingulate cortex, amygdala and striatum. The involvement of such structures highlights the emotional aspects of decision-making and suggests that decision-making may be sensitive to manipulations of the catecholamine systems that innervate these structures. In this study, we investigated the possible role of noradrenaline (NA). *Objective:* We examined the effects of a single oral 80 mg dose of the beta-adrenoceptor blocker, propranolol, on the decision-making of healthy volunteers in a double-blind, placebo-controlled, between-subjects design. *Methods:* Seventeen volunteers ingested a placebo while 15 volunteers ingested propranolol. Visual analogue scales, and self-reported positive and negative ratings, were used to assess subjective changes and mood. Vital signs were also monitored. Seventy-five minutes after treatment, volunteers were asked to make a series of choices between two simultaneously presented gambles, differing in the magnitude of possible gains (i.e. reward), the magnitude of possible losses (i.e. punishment), and the probabilities with which these outcomes were delivered. Volunteers also chose between gambles probing identified non-cognitive biases in human decision-making, namely, risk-aversion when choosing between gains and risk-seeking when choosing between losses. *Results:* Propranolol treatment did not result in gross changes in subjective state or mood in comparison to placebo, but did slow heart rate significantly. Propranolol produced a selective change in volunteers' decision-making; namely, it significantly reduced the discrimination between large and small possible losses when the probability of winning

was relatively low and the probability of losing was high. *Conclusions:* These results suggest that NA modulates the processing of punishment signals when choosing between probabilistic rewards and punishments under conditions of increased arousal.

Keywords Choice · Decision-making · Noradrenaline · Reward · Punishment · Arousal

Introduction

Choosing between actions associated with uncertain rewards and punishments depends upon the functioning of a complex circuitry encompassing cortico-limbic neural stations. These stations are now known to include the orbitofrontal cortex (Bechara et al. 1996; Rogers et al. 1999a, 1999b), anterior cingulate cortex (Bush et al. 2002), and striatum (Elliott et al. 1999). Presumably, the involvement of these structures reflects the fact that decision-making is typically an emotive, as well as cognitive process, in which the decision-maker must weigh the impact of reward cues (those indicating the size of possible gains) against the impact of punishment cues (those indicating the size of possible losses) contingent on different and competing courses of action.

Very little is known about how decision-making, and its underlying neural circuitry, is modulated by the activity of the ascending arousal systems of the reticular core. However, two recent studies have demonstrated that rapid dietary tryptophan depletion alters the decision-making of healthy volunteers, suggesting that central serotonergic activity may be an important neuromodulatory factor (Rogers et al. 1999b, 2003). In the later study, volunteers were asked to choose between simultaneously presented gambles that differed in the magnitude of possible gains, the magnitude of possible losses, and the probabilities with which these outcomes were delivered. Variation in volunteers' preferences suggested that tryptophan depletion affected decision-making by altering the processing of reward cues (Rogers et al. 2002 for

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discussion). In the present study, we studied the role of noradrenaline (NA) in decision-making by investigating the effects of an acute dose of the beta-receptor antagonist propranolol (80 mg) in healthy volunteers using the same procedure.

In terms of postulating a role for NA in mediating decision-making function, a large body of evidence suggests that NA function is important in mediating anxiety (Gray 1987) and subjects' behavioural responses to stressful situations (Redmond and Huang 1979; Neophytou et al. 2001 for review). This evidence includes early findings that stimulation of the locus coeruleus (LC) induces fearful states (Mason and Fibiger 1979), and that the somatic responses to various stressors relate directly to LC activity (Grant et al. 1980; Abercrombie and Jacobs 1987). LC firing rate is increased on the presentation of stimuli conditioned to punishment but not to reward (Jacobs 1987), while depletions of forebrain NA through neurotoxic lesions of the dorsal noradrenergic bundle (Mason and Iversen 1979) have been shown to impair conditioning to discrete aversive cues but to enhance conditioning to aversive contexts (Selden et al. 1990, 1992). At a clinical level, NA function also appears to be compromised in the full range of anxiety disorders (Charney et al. 1984). Against this background, one might postulate that interfering with NA function in healthy individuals might disrupt decision-making by affecting the processing of cues that predict punishment, or the loss of reward. Such a finding would be consistent with evidence that beta-blockade in healthy volunteers seems to have its greatest impact on predominantly negative affect, as seen in impaired consolidation in memory of negatively arousing material (Cahill et al. 1994), and impaired recognition of negative emotion, specifically, sadness, in the human face (Harmer et al. 2001).

On the other hand, the behavioural effects of NA depletions indicate that the role of NA in aversive learning and performance is complex (Selden et al. 1990, 1992 for review). In fact, LC activity has been shown to increase whenever stimulus-reward contingencies change in both appetitive and aversive conditioning procedures (see Sara and Segal 1991) while NA depletion has also been shown to impair acquisition of an appetitive visual discrimination task in which rats choose between instrumental actions to obtain reward (Everitt et al. 1983). Therefore, it also is possible that manipulation of NA might affect decision-making by modulating the processing of cues that predict reward, at least under some conditions.

In general, the complexity of behavioural changes following NA manipulations in both animal models and human volunteers has tended to promote a convergence towards the view that NA has a greater influence on cognitive and emotional functioning under conditions of increased rather than lowered arousal (Amaral et al. 1977; Robbins and Everitt 1995). Subsequent developments have pinpointed NA as an important neural mechanism for protecting the integrity of attentional processes that

need to be maintained in the face of threat or distraction. On the basis that decisions involving larger possible losses are more arousing than those involving smaller losses, and that decisions with a greater chance of losing are more arousing than decisions involving a smaller chance of losing, one might predict that the effects of NA manipulations will reflect interactions between such factors. The present study was conducted to test these initial conjectures.

Materials and methods

Subjects

Thirty-two healthy volunteers between the ages of 18 and 52 took part. Before participating, subjects were given a brief clinical examination by an experienced psychiatrist (Z.B.) in order to check for health factors that would lead to exclusion from the study. These were a history of asthma, cardiac problems or significant current psychiatric illness. The study was approved by the Oxfordshire Psychiatric Research Ethics Committee (OPREC). All volunteers provided written, informed consent and were paid for their participation in the study. Verbal intelligence was estimated with the National Adult Reading Test (NART; Nelson 1982).

Design

The study consisted of a double-blind, placebo-controlled design. Fifteen healthy volunteers received propranolol (80 mg, oral) while seventeen healthy volunteers received placebo. This dose of propranolol was chosen because previous studies have demonstrated significant cognitive and emotional effects in healthy volunteers against placebo in the absence of marked sedation or subjective changes (Currie et al. 1988; Harmer et al. 2001). The propranolol and placebo substances were formulated for consumption in identical gelatin capsules.

Procedure

Each volunteer was assessed after fasting for 2 h and without caffeine intake. Subjective state was assessed using 16 visual analogue scales (VAS) combined to measure mental sedation, physical sedation, tranquility and other feelings (Bond and Lader 1974). Volunteers' mood was assessed in terms of state positive and negative affect (PANAS; see Watson et al. 1988). Volunteers completed the VAS and PANAS assessments before taking the drug and 75 min later, just prior to cognitive testing. Subjects remained at the laboratory for 4 h in total and completed other psychological paradigms (these data are not reported). Heart rate and systolic and diastolic blood pressure were monitored every 30 min.

Decision-making task

Much previous decision-making research has involved asking volunteers to make choices between two "gambles", each consisting of a given probability of winning a certain outcome or losing a certain outcome; for example, a choice between a 0.33 chance to win £100 and a 0.66 chance of losing £20 versus a 0.33 chance to win £240 and a 0.66 chance to lose £60. Variation in preferences, as determined by differences between the gains and losses in each gamble, as well as their respective probabilities, has been researched extensively to examine how choice conforms to, or departs from, what is normatively rational in terms of choices maximising some positive outcome, or "expected value" (Kahne-

Table 1 The eight types of “experimental” gamble resulting from the combination, in a completely crossed design, of two levels of probability, possible gains and possible losses

| Probability | Possible gains | Possible losses |
|-------------|----------------|-----------------|
| High (0.66) | Large (80) | Large (80) |
| | – | Small (20) |
| | Small (20) | Large (80) |
| Low (0.33) | – | Small (20) |
| | Large (80) | Large (80) |
| | Small (20) | Small (20) |
| – | Large (80) | Large (80) |
| – | Small (20) | Small (20) |

man and Tversky 1979; Tversky and Kahneman 1992). The “expected value” of a gamble is the sum of its component values (gains and losses), each weighted by its probability of occurrence. Therefore, the expected value of the above two gambles is $(0.33 \times 100) + (0.66 \times -20) = 19.8$ and $(0.33 \times 240) + (0.66 \times -60) = 39.6$. Thus, the rational choice, in terms of maximising expected value over the longer term is the latter gamble (see Goldstein and Hogarth 1997 for an extensive review).

In this study, each gamble was represented visually by a histogram, the height of which indicated the probability of gaining a given number of points. The possible gains were indicated in green ink above the histogram; possible losses were indicated in red ink underneath the histogram. On each trial, one gamble (coloured yellow) was the control gamble, consisting of a 0.50 probability of winning 10 points and a 0.50 probability of losing 10 points. The alternative “experimental” gamble (coloured blue) varied in the probability of winning which was either high or low (0.66 versus 0.33), possible gains which were either large or small (80 versus 20 points), and possible losses which were either large or small (80 versus 20 points). These variables were combined, in a crossed design, to produce eight trial types (Table 1). Figure 1a shows an “experimental” gamble with a 0.33 chance of winning 80 points (and a 0.66 chance of losing 20 points).

The control and “experimental” gambles appeared randomly on the left or right of the display. The volunteer was required to press the “1” or “2” key on the computer keyboard to indicate choice of the gamble presented on the left or right. The dependent measures were the proportion of choices of the “experimental” over control gamble as a function of its probability of winning, size of the possible gains and size of the possible losses (“proportionate choice”), and the mean deliberation time (ms) for these choices. We also measured volunteers’ discrimination between differences in probability, gains and losses by calculating the absolute difference between the proportion of choices of the “experimental” over the control gamble when each of these factors was high (e.g. when the possible losses were large) and the proportion of choices of the “experimental” gamble when that factor was low (e.g. when the possible losses were small) (Rogers et al. 2002).

As previously described (Rogers et al. 2002), we also included two extra trial types that represented choices between gambles known to be subject to the non-normative biases of risk-aversion and risk-seeking behavior (see Kahneman and Tversky 1979). The first such trial type was a “gains only” trial in which the volunteers were presented simultaneously with a guaranteed win of 40 points versus a 0.5 chance of winning 80 points and a 0.5 chance of losing 0 points (see Fig. 1b). Neither option involved any associated losses. Notice the “expected value” of each gamble in both of these pairs is equal, so that the rational model of choice predicts that volunteers should be indifferent to the options (Kahneman and Tversky 1979). By contrast, in the “losses only” trial type, the volunteers were presented simultaneously with a guaranteed loss of 40 points versus a 0.5 chance of losing 80 points and a 0.5 chance of losing 0 points (see Fig. 1c). Neither option offered any associated gains. For the both the “gains only” trials and the “losses only” trials, the dependent measures were simply proportion of



Fig. 1 a One example trial from the decision-making paradigm consisting of an “experimental” gamble with a 0.33 chance of winning 80 points and a 0.66 chance of losing 20 points versus the control gamble with a 0.50 chance of winning 10 points and a 0.50 of losing 10 points. b A “gains only” trial from the decision-making task consisting of a certain win of 40 points versus 0.50 chance of winning 80 points or 0 points. c A “losses only” trial consisting of a certain loss of 40 points versus a 0.50 chance of a loss of 80 points or 0 points

trials on which the volunteers chose the guaranteed outcome and the associated mean deliberation time (ms) for these choices.

All ten trial types were presented pseudo-randomly within four blocks of trials. At the beginning of each block, volunteers were given 100 experimenter-defined points, and asked to make choices which would increase this amount by as much as possible. These points had no monetary value. Visual feedback was given after each choice and the revised points total was presented for 2 s before the next trial. Across the four blocks, there were eight repetitions of each “experimental” gamble and eight repetitions of the “gains only” and “losses only” trial types.

Data analysis

All the data were analysed with SPSS (Version 11.0; SPSS Inc., Cary, N.C., USA). Heart rate, blood pressure (systolic and

diastolic), mental sedation, physical sedation, tranquillity, and “other feelings” were assessed with repeated measures analysis of variance (ANOVA) with the between-subject factors of treatment group (propranolol versus placebo) and gender, and the within-subject factor of time (baseline versus +75 min). The measures of the decision-making task were the proportions of trials on which volunteers chose the “experimental” over the control gamble (“proportionate choice”), and the deliberation time (ms) associated with these choices. The proportionate choice data were arcsine-transformed, as is appropriate whenever the variance of a measure is proportional to its mean (Howell 1987); however, all of the data reported in the text, figures and tables describe untransformed values. The results were analysed using repeated measures ANOVAs with the between-subject factors of treatment group (propranolol versus placebo) and gender, and the within-subject factors of probability of winning (high versus low), size of possible gains (large versus small) and size of possible losses (large versus small). Discrimination measures for the three factors were analysed by ANOVAs with group as single between-subjects factors. The “gains only” and “losses only” trials were analysed with group and gender as between-subject factors and trial type (“gains only” versus “losses only”) as a single within-subject factor.

Results

The placebo volunteers and the propranolol volunteers were matched in terms of gender [ten males and seven females versus six males and nine females; $\chi^2(1)=1.129$], age (23.59 ± 2.01 versus 20.07 ± 0.81 years) [$F(1,30)=1.24$, $P=0.28$] and estimated verbal IQ (114.53 ± 1.39 versus 116.43 ± 1.64) [$F(1,29)<1.0$].

Physiological effects

Both groups of volunteers showed reductions in heart rate (bpm) between baseline and just prior to testing, 75 min later [$F(1,28)=36.07$, $P<0.0001$]. However, consistent with its effect on beta-adrenoceptors, this effect was greater in volunteers who received propranolol (66.93 ± 2.00 bpm versus 53.87 ± 2.09 bpm) compared to volunteers who received placebo (62.65 ± 2.24 bpm versus 58.47 ± 2.62 bpm) [$F(1,28)=9.84$, $P<0.005$]. Systolic blood pressure was also significantly reduced over this time period [$F(1,28)=10.55$, $P<0.005$]; however, the reduction for the propranolol volunteers (113.47 ± 2.90 versus 107.73 ± 3.87) was not significantly different from that for the placebo volunteers (113.12 ± 3.21 versus 105.06 ± 2.78) [$F(1,28)<1.0$]. Diastolic blood pressure did not change between baseline and testing in either the placebo volunteers (69.47 ± 3.27 versus 66.06 ± 1.68) or the propranolol volunteers (68.53 ± 2.40 versus 69.73 ± 2.42), so that the two-way interaction between treatment group and time was not significant [$F(1,28)=1.71$, $P=0.20$].

Subjective effects

The volunteers who received propranolol tended to report greater but more variable changes in subjective measures than those who received placebo. Consistent with other published studies (Harmer et al. 2001), there was little

Table 2 State positive and negative affect (PANAS; Watson et al. 1988) in healthy volunteers treated with placebo ($n=17$) and 80 mg propranolol ($n=15$)

| Group | State +ve affect at 0 h | State -ve affect at 0 h | State +ve affect at +75 min | State -ve affect at +75 min |
|-------------------|-------------------------|-------------------------|-----------------------------|-----------------------------|
| Placebo | 29.76 \pm 1.39 | 11.82 \pm 0.40 | 28.24 \pm 1.52 | 10.81 \pm 0.28 |
| Propranolol/80 mg | 27.67 \pm 1.66 | 12.80 \pm 0.72 | 24.47 \pm 1.40 | 10.93 \pm 0.45 |

sign that this dose of propranolol (80 mg) produces marked subjective effects. All volunteers reported significantly increased mental sedation between baseline and 75 min later [$F(1,28)=4.88$, $P<0.05$]. This increase was only non-significantly greater in the propranolol compared to placebo volunteers ($31.65\pm 12.71\%$ versus $17.41\pm 11.93\%$) [$F(1,28)<1.0$]. Physical sedation remained largely unchanged in both the placebo and the propranolol volunteers ($9.95\pm 8.52\%$ versus $17.11\pm 12.08\%$) [$F(1,28)<1.0$]. Feelings of tranquillity were slightly reduced in the placebo volunteers ($8.02\pm 7.15\%$) but increased in the propranolol volunteers ($9.81\pm 11.01\%$) [$F(1,30)<2.81$, $P=0.11$]. “Other feelings” increased between baseline and 75 min [$F(1,28)=2.28$, $P=0.14$], but to a more variable extent in the propranolol compared to the placebo volunteers ($32.78\pm 26.14\%$ versus $5.91\pm 8.08\%$) [$F(1,28)=1.02$, $P=0.32$].

Self-reported mood was also relatively unchanged. In both sets of volunteers, positive affect and negative affect declined significantly between baseline and cognitive testing [$F(1,28)=12.18$, $P<0.005$ and $F(1,27)=14.37$, $P<0.005$, respectively]. However, there was no evidence that these changes were significantly reduced or increased in the propranolol compared to the placebo volunteers [$F(1,28)=1.41$, $P=0.25$ and $F(1,27)<1.01$, $P=0.31$ respectively.] (see Table 2) One rating of negative affect/PANAS at +75 min was missing for one propranolol volunteer.

Probability, wins and losses

Proportionate choice

All volunteers chose the “experimental” gamble significantly more often when its probability of winning was high compared to when it was low [$F(1,28)=229.00$, $P<0.0001$]. Overall, this pattern of choices was not changed in the propranolol volunteers (0.75 ± 0.03 versus 0.26 ± 0.04) compared to the placebo volunteers (0.77 ± 0.02 versus 0.22 ± 0.03) [$F(1,28)<1.00$]. All volunteers chose the “experimental” gamble significantly less often when its possible losses were large compared to when they were small [$F(1,28)=120.14$, $P<0.0001$]. This pattern of decision-making was not altered in the propranolol volunteers compared to the placebo volunteers when the probability of winning was high, but was significantly altered when the probability of winning was low, as

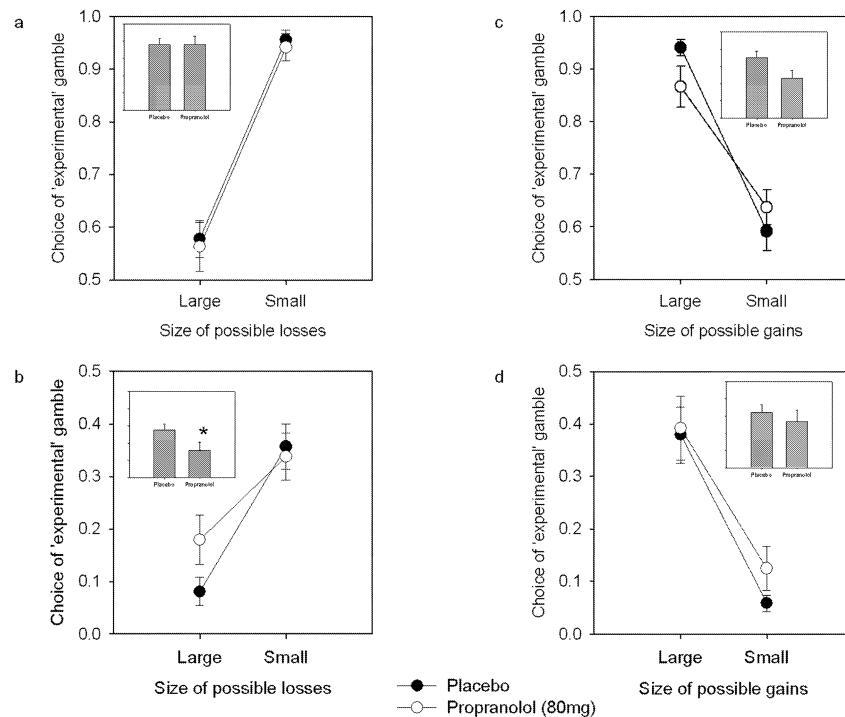


Fig. 2 Proportion of choices of the “experimental” over the control gamble by the placebo and propranolol volunteers (80 mg). **a** Large versus small possible losses when the probability of winning was high (inset: mean absolute difference between the proportions of choices of the “experimental” over the control gamble when its possible losses were large and small). **b** Large versus small possible losses when the probability of winning was low (inset: the mean absolute difference between the proportions of choices of the “experimental” over the control gamble when its possible losses were large and small). **c** Large versus small possible gains when the probability of winning was high (inset: the mean absolute

difference between the proportions of choices of the “experimental” over the control gamble when its possible gains were large and small). **d** Large versus small possible gains when the probability of winning was low (inset: the mean absolute difference between the proportions of choices of the “experimental” over the control gamble when its possible gains were large and small). Treatment (placebo versus propranolol) × probability of winning (high versus low) × size of possible losses (large versus small): $F(1,28)=4.48$, $P<0.05$; simple interaction effect when probability of winning was low: treatment × size of possible gains: $F(1,28)=4.04$, $P<0.05$; $*F(1,30)=4.26$, $P<0.05$

evidenced by a significant three way interaction between treatment group, probability of winning and size of possible losses [$F(1,28)=4.48$, $P<0.05$]. Subsequent analyses of the simple interaction effects demonstrated that the propranolol volunteers reduced their choice of the “experimental” gamble in response to larger possible losses to the same extent as the placebo volunteers when the associated probability of winning was high [see Fig. 2a; $F(1,28)<1.0$] but not when the probability of winning was low [see Fig. 2b; $F(1,28)=4.04$, $P<0.05$].

Finally, all volunteers chose the “experimental” gamble significantly more often when its possible gains were large compared to when its possible gains were small [$F(1,28)=83.2$, $P<0.0001$], and to a similar extent in both groups [$F(1,28)=1.14$, $P=0.29$]. This pattern of choices was not significantly changed in the propranolol volunteers (0.63 ± 0.04 versus 0.38 ± 0.03) compared to the placebo volunteers (0.66 ± 0.03 versus 0.33 ± 0.02) as a function of the probability of winning on the “experimental gamble” [see Fig. 2c versus Fig. 2d; $F(1,28)<1.00$].

Additional analyses showed that the propranolol and placebo volunteers showed comparable discrimination

between the size of possible losses when the probability of winning on the “experimental” gamble was high [see Fig. 2a, inset; $F(1,30)<1.00$] but not when the probability of winning was low [see Fig. 2b, inset; $F(1,30)=4.26$, $P<0.05$]. On the other hand, the propranolol volunteers did show a trend towards reduced discrimination between different sizes of possible gains when the probability of winning on the “experimental” gamble was high [Fig. 2c, inset; $F(1,30)=3.7$, $P=0.06$] but not when it was low [Fig. 2d, inset; $F(1,30)<1.0$].

Overall, male volunteers tended to choose the “experimental” gamble as often as female volunteers (0.51 ± 0.02 versus 0.49 ± 0.02) [$F(1,28)<1.0$]. There were no significant interactions involving gender, treatment group or any other task variable. Repeat analyses, including age, estimated verbal IQ, cardiovascular and subjective measures as covariates, did not alter the pattern of data reported above or the central result that the propranolol volunteers showed reduced discrimination between the size of possible losses when the probability of winning on the “experimental” gamble was low compared to the placebo volunteers.

Deliberation times

Volunteers were significantly faster to make their choices when the probability of winning on the “experimental” gamble was high compared to when it was low [$F(1,28)=7.57$, $P=0.01$]. This effect was no greater in the propranolol volunteers (2088 ± 243 ms versus 2230 ± 285 ms) compared to the placebo volunteers (1794 ± 120 ms versus 2070 ± 162 ms) [$F(1,28)<1.0$]. Overall, volunteers made significantly slower choices when the “experimental” gamble was associated with large possible losses compared to small possible losses [$F(1,28)=13.69$, $P=0.001$]. There was no difference in the size of this effect in the propranolol volunteers (2250 ± 263 ms versus 2068 ± 260 ms) compared to placebo volunteers (2021 ± 141 ms versus 1842 ± 132 ms) [$F(1,28)<1.0$]. Finally, all volunteers made significantly slower choices when the “experimental” gamble was associated with larger possible gains compared to smaller possible gains [$F(1,28)=11.20$, $P<0.005$], and to a similar extent in the propranolol volunteers (2266 ± 290 ms versus 2052 ± 232 ms) compared to the placebo volunteers (1980 ± 140 ms versus 1883 ± 128 ms) [$F(1,28)=2.06$, $P=0.16$]. Finally, the propranolol volunteers tended to make their choices only slightly slower than the placebo volunteers (2159 ± 260 ms versus 1932 ± 132 ms) [$F(1,28)<1.0$], as did female volunteers compared to male volunteers (2103 ± 253 ms versus 1974 ± 127 ms) [$F(1,28)<1.0$].

“Gains only” versus “losses only” trials

Proportionate choice

Volunteers chose the guaranteed outcome significantly more often on the “gains only” trials (offering a choice between a certain gain of 40 points and a 0.50 chance of 80 points or 0 points) than on the “losses only” trials (offering a certain loss of 40 points or a 0.50 chance of a loss of 80 points or 0 points) [$F(1,28)=68.95$, $P<0.0001$]. However, this pattern of choices (risk-aversion when choosing between gains and risk-seeking when choosing between losses) was not significantly different in the propranolol volunteers [Fig. 3a; $F(1,28)<1.00$].

Deliberation times

Volunteers were significantly quicker to make their choices on the “gains only” trials compared to the “losses only” trials [$F(1,28)=56.98$, $P<0.0001$], with no difference in the size of this effect in the propranolol volunteers (1760 ± 310 ms versus 2948 ± 300 ms) compared to placebo volunteers (1593 ± 165 ms versus 3118 ± 339 ms) [see Fig. 3b; $F(1,29)<1.00$].

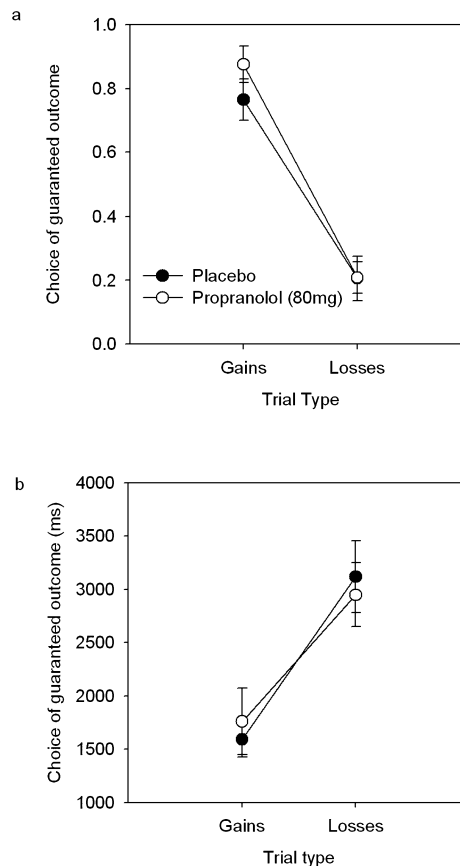


Fig. 3 **a** Proportion of choices of the guaranteed outcome by the placebo volunteers and the propranolol volunteers for the “gains only” trials and the “losses only” trials. **b** Mean deliberation times (ms) for the placebo and propranolol volunteers for the “gains only” and “losses only” trials

Discussion

The results of this study demonstrate that a single 80 mg dose of the non-specific beta-adrenoreceptor blocker, propranolol, alters the decision-making of healthy volunteers; namely, it significantly attenuated volunteers’ discrimination between the magnitude of possible losses in situations where the probability of winning was relatively low and the probability of suffering losses was relatively high. It is unlikely that this effect can be attributed to generalised sedation since, consistent with previously published studies (Currie et al. 1988; Harmer et al. 2001), there was little sign of significant changes in mood (measured here with the PANAS scales; Watson et al. 1988), or subjective experience (measured by visual analogue scales; Bond and Lader 1974) in the propranolol compared to the placebo-treated volunteers. By contrast, propranolol did produce a significant slowing of heart rate, consistent with its action as a hypotensive agent (Cruickshank and Prichard 1988). Therefore, these data implicate NA mechanisms in our developing understanding of the neural and neurochemical basis of human risky choice.

Propranolol had its most marked effects on the processing of possible losses during performance of the decision-making paradigm, suggesting that beta-adrenoceptor blockade had the consequence of attenuating the processing of punishment cues in the context of choosing between actions associated with probabilistic outcomes. Additionally, there is some indication that the propranolol volunteers showed reduced discrimination between the different levels of possible gains when the probability of winning on the “experimental” gamble was high. However, this effect (see Fig. 2c) was not underpinned by any statistically significant interactions between treatment, probability of winning and the size of possible gains. Therefore, these data clearly leave open the possibility that an acute 80 mg dose of propranolol also affects the processing reward information, as well as punishment information.

Previously, we have found that rapid depletion of dietary tryptophan attenuated discrimination between different magnitudes of possible gains while leaving the discrimination between possible losses unaffected (Rogers et al. 2002). It might be argued that the results of the present study may also be due to changes in serotonergic activity through propranolol’s affinity for 5-HT_{1A} receptors. However, previous research has shown that the affinity of propranolol for these receptors at this dose is relatively limited (Upadhyaya et al. 1990). Therefore, taken together, these two studies suggest that human risky choice is sensitive to 5-HT and NA neuromodulation, perhaps with the former playing a greater role in the processing of reward cues and the latter playing a clearer role in the processing of punishment cues, at least under some conditions. Further investigation is required to establish the sites of action for propranolol’s effect and, in particular, to examine the question of whether they are mediated by central versus peripheral beta-adrenoceptor blockade (cf. Currie et al. 1988; O’Carroll et al. 1999; Beversdorf et al. 2002).

As noted above, several theoretical approaches seeking to unify our understanding of the various, seemingly inconsistent, behavioural changes seen after manipulation of the NA system propose that NA is central to mediating coping responses in the face of distraction or stress (Robbins and Everitt 1995). Consistent with this perspective, we have found that the changes in the processing of possible losses associated with propranolol treatment were only apparent when the probability of winning on the “experimental” gamble was low and the probability of losing was relatively high. In general, volunteers’ deliberation times were significantly longer on such trials compared to those trials on which the probability of winning was high and the probability of losing was low (2145 ± 157 ms versus 1932 ± 131 ms; $P < 0.01$), indicating that the decision-making process was protracted when the balance of probabilities was stacked against the decision-maker. Under these conditions, large possible losses produced a smaller reduction in the proportionate choice of the “experimental” gamble in propranolol compared to the placebo volunteers (see Fig. 2b), suggesting that beta-

adrenoceptor blockade attenuated the impact of punishment cues under conditions of greater choice difficulty. By contrast, there was no difference in the effects of larger possible losses on the choice of the “experimental” gamble in easier choices; namely, on trials on which the probability of winning was high and the probability of losing was low (Fig. 2a).

Normative accounts of decision-making emphasise that adaptive choice depends upon effectively integrating multiple but conflicting cues to action with a view to maximising some “value” in the longer term (Goldstein and Hogarth 1997). In the present study, these cues included different levels of possible gains (or reward), different levels of possible losses (or punishment), as well as varying levels of probability with which these outcomes were delivered. However, there is an extensive literature detailing how, in many situations, the combination of these cues, in tandem with certain contextual factors, can lead to highly non-normative decisions (e.g. Kahneman and Tversky 1979). These situations are exemplified by the “gains only” and “losses only” trials of the current study in which volunteers were required to choose between certain gains versus gambles to earn greater gains or no gains (inducing risk-aversion), or choose between certain losses versus gambles to suffer no loss or still larger losses (inducing risk-seeking decisions). On these trials, there was no indication that propranolol altered proportionate choice or deliberation times compared to placebo. Therefore, while the results suggest that beta-adrenoceptor blockade may interfere with choices involving high probabilities of relatively high levels of punishment, there was little evidence that, in extremis, non-normative features of decision-making were disturbed.

Several lines of evidence indicate that decision-making involves the interaction of a wide cortical and sub-cortical network encompassing the orbitofrontal cortex, the anterior cingulate cortex and the striatum (Bechara et al. 1996; Rogers et al. 1999b; Bush et al. 2002). There is also evidence to implicate the amygdala (Bechara et al. 1999). The results of the present study suggest that beta-adrenoceptor blockade by propranolol alters the neuromodulation of this circuitry and, specifically, alters the functioning of that portion of the circuitry mediating the impact of aversive cues in human choice. The finding is broadly consistent with propranolol’s mildly anxiolytic effects (Mealy et al. 1996). For the moment, we have little information about which structures are modulated by this treatment to produce these effects although there is some evidence that NA modulates the processing of aversive signals within the amygdala (Ellis and Kesner 1983; Selden et al. 1990). Further work, perhaps combining pharmacological challenge and functional brain-imaging technologies, is needed to establish the sites at which the various monoaminergic systems modulate the cognitive and emotional constituent parts of decision-making function.

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