The Role of Serotonin in Nonnormative Risky Choice: The Effects of Tryptophan Supplements on the ''Reflection Effect'' in Healthy Adult Volunteers

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Abstract

■ Risky decision-making involves weighing good and bad outcomes against their probabilities in order to determine the relative values of candidate actions. Although human decision-making sometimes conforms to rational models of how this weighting is achieved, irrational (or nonnormative) patterns of risky choice, including shifts between risk-averse and risk-seeking choices involving equivalent-value gambles (the ''reflection effect''), are frequently observed. In the present experiment, we investigated the role of serotonin in decision-making under conditions of uncertainty. Fifteen healthy adult volunteers received a treatment of 3 g per day of the serotonin precursor, tryptophan, in the form of dietary supplements over a 14-day period, whereas 15 age- and IQ-matched control volunteers received a matched placebo substance. At test, all participants completed a risky decision-making task involving a series of choices between two simultaneously presented gambles, differing in the magnitude of their possible gains, the magnitude of their possible losses, and the probabilities with which these outcomes were delivered. Tryptophan supplements were associated with alterations in the weighting of gains and small losses perhaps reflecting reduced loss-aversion, and a marked and significant diminution of the reflection effect. We conclude that serotonin activity plays a significant role in nonnormative risky decision-making under conditions of uncertainty. ■

INTRODUCTION

Effective decision-making involves identifying the values of candidate actions given the uncertainty of their good and bad payoffs. Rational, or normative, models posit that decision-makers should select actions with the maximal expected value based upon the aggregated values of their good and bad consequences, each weighted by its probability of occurrence (Bernoulli, 1954; von Neumann & Morgenstern, 1944). However, although these models have enhanced our understanding of microeconomic choices (Goldstein & Hogarth, 1997), it is well known that everyday human decision-making involves a variety of intervening heuristics, and nonlinear transformations of values into utilities (Khaneman & Tversky, 1979) and actual probabilities into subjectively distorted counterparts (Khaneman & Tversky, 1979; Savage, 1954).

One example of nonnormative choice is the ''reflection effect.'' Confronted with a choice between a certain gain and a 50/50 gamble to win twice that gain or no gain at all, decision-makers typically choose the guaranteed gain, exhibiting risk-aversion. By contrast, changing the sign of these outcomes to produce a choice between a certain loss and a 50/50 gamble offering twice that loss or no loss at all, induces a preference reversal for the risk-seeking option (Shafir & Tversky, 1995). Descriptive accounts attribute the reflection effect to the different ways that actual things of value, such as goods or money, related to subjective value, or ''utility'', and the fact that the values of outcomes are judged against the decision-maker's current reward state, or ''reference point''. Greater gains relative to a given reference point produce only diminishing increases in subjective value, reflecting a concave function between the two, and utility, and favouring risk-averse choices that ensure substantial increases in utility. By contrast, greater losses relative to the same reference point produce diminishing reductions in subjective value, reflecting a convex function between value and utility, and favouring risky choices that, even if unsuccessful, produce only slightly greater reductions in utility compared to riskless choices (Khaneman & Tversky, 1979).

Neurophysiological experiments have begun to identify the circuits that represent expected value, and its reward magnitude and probability components (Tobler, O'Doherty, Dolan, & Schultz, 2007; Montague, King-Casas, & Cohen, 2006; Yacubian et al., 2006; Glimcher, 2001). In humans, neural activity within the ventromedial prefrontal cortex and the ventral striatum (including the nucleus accumbens) code the probability of gains and their magnitudes, respectively (Knutson, Taylor, Kaufman, Peterson,

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& Glover, 2005). Similarly, activity within the ventral striatum and a region ventral to the pregenual cingulate gyrus may play a role in representing positive expected values in the context of choices between simple gambles (Rolls, McCabe, & Redoute, 2008; Yacubian et al., 2006); negative expected values may be represented within the amygdala (Yacubian et al., 2006). These data are consistent with proposals that the value and probability representations involved in risky choice involve a circuitry, and its dopaminergic modulation (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Schultz, Tremblay, & Hollerman, 2000), that is pivotal to reinforcement learning (Schultz, 2006) and the experience of affective states (Damasio et al., 2000).

Variation in the functioning of corticolimbic circuitry may also be implicated in aspects of nonnormative choice. Loss-aversion, involving the greater salience of losses compared to gains and an unwillingness to accept single 50/50 gambles yielding gains only marginally greater than losses, may involve increased activity in response to gains but decreased activity in response to losses within a circumscribed circuit incorporating the ventromedial prefrontal cortex, the insula, and the ventral striatum (Dreher, 2007; Tom, Fox, Trepel, & Poldrack, 2007).

Despite these advances, little is known about the role of monoamines in modulating risky choices based on calculations of expected value, or departures from normative patterns of decision-making such as the reflection effect. The neural circuits most likely to code expected value are innervated by the ascending serotonin projections arising in the raphe nuclei, and the cognitive mechanism subserved by these areas are known to be profoundly influenced by serotonergic modulation (Walker, Mikheenko, Argyle, Robbins, & Roberts, 2006; Clarke et al., 2005; Rogers et al., 1999).

Recently, we have developed a method for investigating the way that decision-makers combine information about gains and losses when choosing between actions associated with uncertain outcomes (Rogers, Wakeley, Robson, Bhagwagar, & Makela, 2007; Morgan, Impallomeni, Pirona, & Rogers, 2006; Rogers, Lancaster, Wakeley, & Bhagwagar, 2004; Rogers, Ramnani, et al., 2004; Rogers et al., 2003). Subjects make a series of choices between two simultaneously presented gambles, one of which consists of .5 probability of winning or losing a certain amount (and has 0 expected value), while the other gamble varies in the magnitude of its gains, the magnitude of its losses, and the probabilities with which these outcomes are delivered (giving rise to expected values that vary between positive and negative values). Choices of the high-variant gamble over the 0-expected value gamble can provide information about the weight that participants attribute to gains, losses, and probability cues when making risky choices. The task also includes choices between certain gains and losses that allow us to examine the neurochemical bases of the ''reflection effect.''

Using this procedure, we have investigated the effects of rapid dietary depletion of the serotonin precursor, L-tryptophan, on risky choice (Rogers et al., 2003). Tryptophan depletion reduced healthy adult volunteers' attention toward information about possible gains, suggesting that serotonin plays a role in the processing of rewards while deliberating between risky choices. By contrast, there was no evidence that tryptophan depletion altered the reflection effect; participants who underwent tryptophan depletion remained as risk-averse when choosing between a certain gain and a 50/50 gamble to win twice that gain or no gain at all as participants who underwent the control procedure. Similarly, there was no change in risk-seeking choices between a certain loss and a 50/50 gamble offering twice that loss or no loss at all.

The above considerations suggest that increasing serotonergic activity should increase participants' discrimination between large and small gains when making risky choices. Here, we report the effects of 14 days of tryptophan supplements on risky decision-making in healthy adults. Using a more sensitive version of the task, we provide evidence that serotonin plays a significant role in choices involving expected value, and in one important violation of normative choice, specifically, the reflection effect.

METHODS

Participants

Thirty healthy volunteers (14 men and 16 women), aged between 18 and 40 years, took part in the study. Participants were recruited using advertisements placed in University departments and were screened to exclude those with a current or previous psychiatric disorder (assessed using the Structured Clinical Interview for DSM-IV; First, Spitzer, Gibbon, & Williams, 2002) or significant physical illness. All participants gave their written consent to participate in the study, which was approved by the local ethics committee. Verbal IQ was estimated with the National Adult Reading Test (Nelson, 1982).

Design

The study consisted of a between-subject, double-blind, placebo-controlled design. Participants were randomized to receive three daily supplements of 1 g L-tryptophan or an equivalent placebo for 14 days. Three daily supplements of 1 g tryptophan sustain tryptophan hydroxylase close to saturation over a 24-hr period (Young & Gauthier, 1981). We chose a 14-day treatment because treatments of comparable duration have been shown to produce changes in social behavior in healthy adults (Moskowitz, Pinard, Zuroff, Annable, & Young, 2001). This treatment period also allowed us to avoid the paradoxical anxiogenic effects that have been reported to follow acute serotonergic manipulations in animals (Burghardt, Sullivan, McEwen, Gorman, & LeDoux, 2004),

in healthy volunteers (Attenburrow et al., 2003; Harmer et al., 2003), and in clinical populations (Kent, Coplan, & Gorman, 1998). The premenstrual week was avoided for the study period for female participants. Participants completed the risky choice task on the 14th day, alongside tests of emotional expression recognition, emotional categorization and memory, attentional orienting (''dot-probe''), and emotional startle reflex (Murphy, Longhitano, Ayres, Cowen, & Harmer, 2006).

Subjective State Measurements

Participants completed the state versions of the Positive and Negative Affect Scale (Watson, Clark, & Tellegen, 1988) and the Spielberger State Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1983) at baseline and on the 14th day.

Risky Choice Task

On each trial, participants chose between two simultaneously presented gambles. Each gamble was visually represented by a histogram, the height of which indicated the probability of gaining a given number of points (see Figure 1A). The possible gains were indicated in green ink above the histogram and the possible losses were indicated in red ink below the histogram. One gamble (colored yellow) was always the control gamble, which had a .50 probability of winning 10 points and a .50 chance of losing 10 points and, therefore, an expected value of 0. The alternative ''experimental'' gamble (colored blue) varied in the probability of winning which was either high or low (.60 vs. .40), possible gains which were either large or small (70 vs. 30 points) and possible losses which were either large or small (70 vs. 30 points). These variables were crossed to produce eight trial types with expected values that varied between −30 and +30 (see Table 1). Figure 1A shows an ''experimental'' gamble with a .40 probability of winning 70 points (and a .60 probability of losing 30 points).

The control and the ''experimental'' gamble appeared randomly on the left or right of the screen. The participants were required to press the ''1'' or ''2'' key to indicate whether they wanted to choose the left or right gamble, respectively. Dependent measures were the proportion of choices of the ''experimental'' over the control gamble as a function of its probability of winning, size of possible gains and the size of possible losses (''proportionate choice''), and the mean deliberation time (msec) for these choices.

Models of Nonnormative Risky Choice: The ''Reflection Effect''

Two trial types were included that represented choices known to be subject to the nonnormative biases of risk-averse and risk-seeking choices when confronted with certain wins or certain losses (Shafir & Tversky, 1995). The first type was a ''gains-only'' trial, in which participants were asked to choose between a guaranteed win of 30 points and a gamble with a .5 chance of winning 60 points and a .5 chance of winning 0 points (Figure 1B).

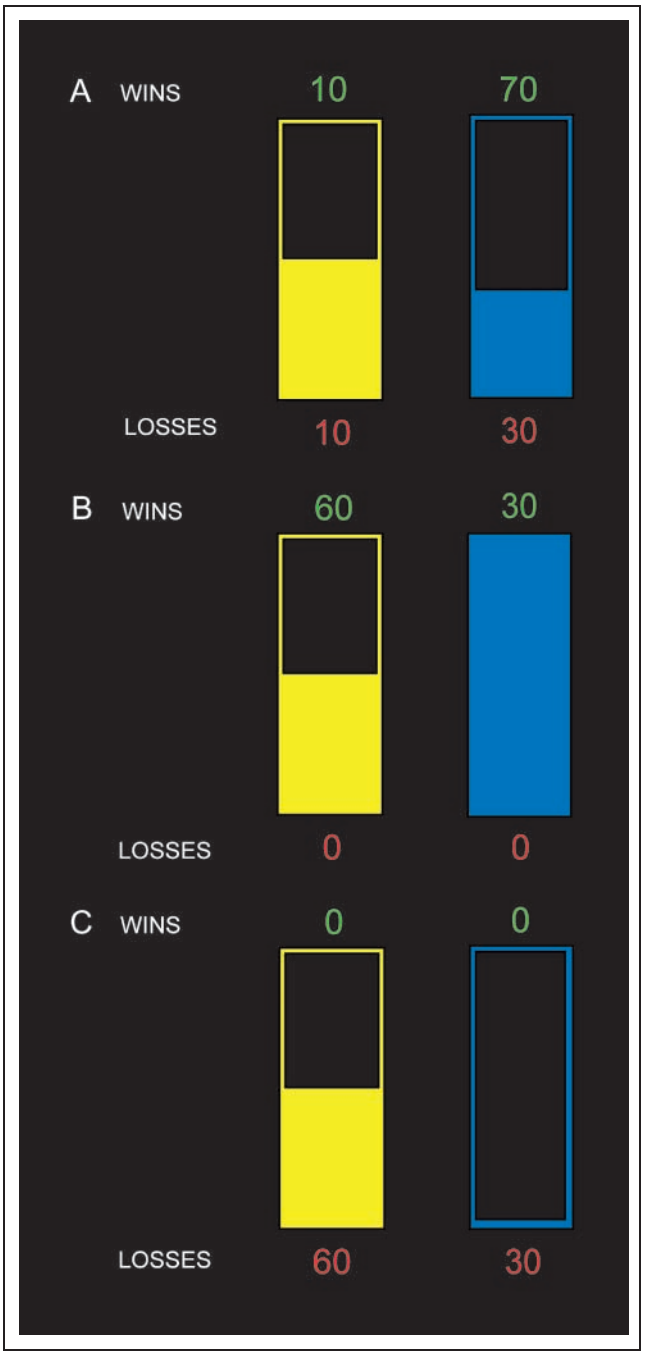

Figure 1. (A) An example visual display from the decision-making task, consisting of an ''experimental'' gamble with a .40 chance of winning 70 points and a .60 probability of losing 30 points versus the control gamble with a .50 chance of winning 10 points and a .50 of losing 10 points. (B) A ''gains-only'' trial consisting of a certain win of 30 points and a gamble with a .50 probability of winning 60 points or 0 points. (C) A ''losses-only'' trial consisting of a certain loss of 30 points and a gamble with a .50 probability of losing of 60 points or 0 points.

Table 1. The Eight Trial Types of ''Experimental'' Gamble Resulting from the Combination of Two Levels of Probability, Magnitude of Possible Gains and Magnitude of Possible Losses

Probability	*Possible Gains*	*Possible Losses*	*Expected Value*[a]	*Placebo*	*Tryptophan*
High (.60)	Large (70)	Large (70)	14	0.78 ± 0.06	0.74 ± 0.07
		Small (30)	30	0.93 ± 0.02	0.88 ± 0.05
	Small (30)	Large (70)	−10	0.49 ± 0.07	0.35 ± 0.08
		Small (30)	6	0.91 ± 0.03	0.88 ± 0.05
Low (.40)	Large (70)	Large (70)	−14	0.19 ± 0.05	0.20 ± 0.04
		Small (30)	10	0.52 ± 0.09	0.44 ± 0.08
	Small (30)	Large (70)	−30	0.18 ± 0.06	0.14 ± 0.04
		Small (30)	−6	0.15 ± 0.05	0.31 ± 0.05*

[a]The ''expected value'' for each gamble equals the sum of its gains and losses, each weighted by their probability of occurrence (Shafir & Tversky, 1995). These values vary between +30 and −30 points, with a mean of 0.

*$F(1, 26) = 8.23$, $p < .001$.

Neither option involved losses. By contrast, the second type was a ''losses-only'' trial, in which participants were asked to choose between a guaranteed loss of 30 points and a gamble with a .5 chance of losing 60 points and a .5 chance of losing 0 points (Figure 1C). Neither option involved gains.

Within both the ''gains-only'' and ''losses-only'' trial types, the expected value of each gamble was equal; however, decision-makers usually exhibit a marked risk-aversion in the former case (i.e., they choose the guaranteed gain of 30 points) but marked risk-seeking behavior in the latter case (i.e., they choose the gamble with a .5 chance of losing 60 points and a .5 chance of losing 0 points) (Shafir & Tversky, 1995). For both the ''gains-only'' and ''losses-only'' trials, the dependent measures were the proportion of trials on which the participants chose the guaranteed outcome and the associated mean deliberation time (msec) for making decisions on these trials.

The 10 trial types described above were presented pseudorandomly within four blocks of 20 trials. Across the four blocks, there were eight repetitions of each ''experimental'' gamble and eight repetitions of each of the ''gains-only'' and the ''losses-only'' trial types. At the beginning of each block of trials, participants were given 100 experimenter-defined points and asked to make choices that 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 sec before the next trial. At the end of each block, the participants were given a final score for that block.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Scientists version 15.0 (SPSS). Age and verbal IQ scores were analyzed with multifactorial analysis of variance (ANOVA) with the two between-subject factors of treatment (placebo vs. tryptophan) and sex. Subjective effects data were analyzed with repeated measures ANOVAs with the between-subject factors of treatment and sex, and the within-subject factor of time (pretreatment vs. posttreatment).

For the risky choice task, the proportionate choice data of the ''experimental'' gamble over the control gamble were arcsine-transformed, as is appropriate whenever the variance of a measure is proportional to its mean (Howell, 1987); however, the data reported in the text, figures, and tables show untransformed values. These data, and the mean deliberation times, were analyzed with repeated measures ANOVAs with the two between-subject factors of treatment and sex, and the three within-subject factors of probability of winning (high vs. low), size of possible gains (large vs. small), and size of possible losses (large vs. small). Additionally, participants' choice of the ''experimental'' gamble as a function of its expected value was investigated by ANOVAs with the between-subject factors of sex and treatment, and the single within-subject factor of expected value (−30, −14, −10, −6, +6, +10, +14, and +30). Finally, the ''gains-only'' and ''losses-only'' trials were analyzed with repeated measures ANOVAs with the two between-subject factors of sex and treatment, and the within-subject factor of trial type (''gains-only'' trials vs. ''losses-only'' trials).

RESULTS

Participants who received the placebo and participants who received the tryptophan supplements did not differ in terms of their age [24.60 ± 0.89 vs. 26.47 ± 1.21; $F(1, 26) = 1.75$] or their estimated verbal IQ [106.93 ± 1.83 vs. 106.21 ± 1.76; $F < 1.00$].[1]

Table 2. State Anxiety, Positive Affect, and Negative Affect

	State Anxiety (STAI)		*State Positive Affect (PANAS)*		*State Negative Affect (PANAS)*	
	Baseline	*14 Days*	*Baseline*	*14 Days*	*Baseline*	*14 Days*
Placebo	35.97 ± 1.86	33.00 ± 2.16	27.84 ± 1.77	25.96 ± 2.60	12.54 ± 0.93	12.27 ± 0.70
Tryptophan	30.31 ± 2.24	30.60 ± 3.00	30.03 ± 1.67	28.22 ± 1.70	13.57 ± 1.44	13.55 ± 2.20

State Anxiety and Affect

Overall, state anxiety was very slightly reduced from baseline over the 14-day treatment period (33.14 ± 1.45 vs. 31.80 ± 1.85) but not significantly so [$F(1, 26) = 1.08$]. There were no distinctive changes in state anxiety in those participants who received the tryptophan supplements compared to those who received the placebo (see Table 2) [$F(1, 26) = 1.57$]. Overall, state positive and state negative affect were also marginally diminished over 14 days [28.93 ± 1.22 vs. 27.09 ± 1.55; 13.05 ± 0.86 vs. 12.92 ± 1.15, respectively; $F(1, 26) < 2.88$]; however, no more so following treatment with tryptophan supplements compared to placebo (Fs < 1.00; see Table 2).

Crucially, there were no significant between-group differences in any of the above measures of anxiety or affect at the end of the 14-day period (all Fs < 1.00; Table 2).

Risky Decision-making Task

Proportionate Choice

Participants chose the ''experimental'' gamble significantly more often when its probability of winning was high compared to when its probability of winning was low [0.75 ± 0.02 vs. 0.27 ± 0.03; $F(1, 26) = 157.75$, $p < .001$]. However, this pattern of choices was not significantly altered in those participants who received tryptophan compared to those who received placebo (Table 3) [$F(1, 26) = 1.91$, $p = .18$].

Overall, participants chose the ''experimental'' gamble significantly more often when its possible gains were large compared to when they were small [0.59 ± 0.02 vs. 0.43 ± 0.03; $F(1, 26) = 34.05$, $p < .001$], and significantly less often when its possible losses were large compared to when they were small [0.39 ± 0.03 vs. 0.63 ± 0.02; $F(1, 26) = 46.49$, $p < .001$]. Treatment with tryptophan did not significantly influence either of these effects compared to treatment with placebo (Fs < 1.00; Table 3).

However, tryptophan supplements did alter the way participants combined information about gains and losses when making risky choices, reflected in a significant three-way interaction between treatment, the size of possible gains, and the size of possible losses [$F(1, 26) = 5.46$, $p < .05$]. Analysis of the simple interaction effects showed that, following treatment with the placebo, participants chose the ''experimental'' gamble more often when its gains were large compared to when they were small, and less often when its losses were large compared to when they were small (as described above). However, these effects were *additive*, or independent, of each other (see Figure 2A), reflected in a nonsignificant two-way interaction between size of possible gains and the size of possible losses ($F < 1.00$). By contrast, following treatment with tryptophan, participants showed increased choice of the ''experimental'' gamble when its possible gains *and* losses were both small (see Figure 2B), reflecting a pattern of *interactive* effects and a significant two-way interaction between the size of possible gains and the size of possible losses [$F(1, 13) = 6.14$, $p < .05$].

Deliberation Times

Participants were significantly faster to make their decisions when the ''experimental'' gamble was associated with a high probability of winning compared to a low probability of winning [2617 ± 180 vs. 2839 ± 171 msec; $F(1, 26) = 5.61$, $p < .05$]. This facilitatory effect was not changed following tryptophan supplements compared to placebo ($F < 1.00$; see Table 4). Deliberation times were not markedly altered when the ''experimental'' gamble was associated with large compared to small possible gains [2747 ± 183 vs. 2709 ± 167 msec;

Table 3. Proportionate Choice of ''Experimental'' Gamble as a Function of High vs. Small Probability of Winning, Large vs. Small Possible Gains, and Large vs. Small Possible Losses

	Probability of Winning		*Size of Possible Gains*		*Size of Possible Losses*	
Group	*High*	*Low*	*Large*	*Small*	*Large*	*Small*
Placebo	0.78 ± 0.03	0.26 ± 0.04	0.61 ± 0.03	0.43 ± 0.04	0.41 ± 0.04	0.63 ± 0.03
Tryptophan	0.72 ± 0.04	0.27 ± 0.04	0.57 ± 0.04	0.42 ± 0.03	0.36 ± 0.04	0.63 ± 0.04

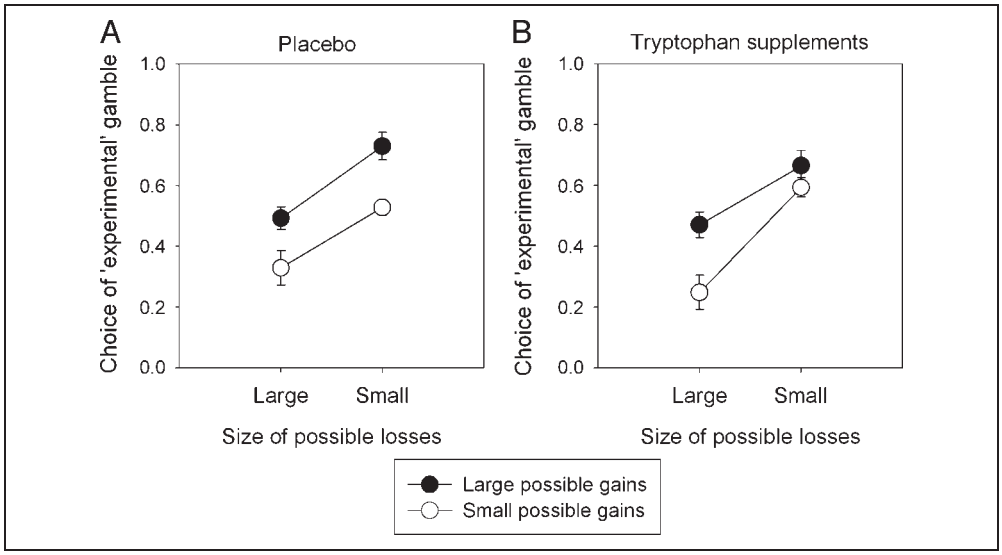

Figure 2. Proportion of choices of the ''experimental'' gamble over the control gamble as a function of large versus small possible gains and large versus small possible losses. (A) Fifteen healthy adult participants who received placebo. (B) Fifteen healthy adult participants who received tryptophan supplements (3 daily treatments of 1 g) for 14 days. Treatment (placebo vs. tryptophan supplements) × Size of possible gains (large vs. small) × Size of possible losses (large vs. small): $F(1, 26) = 5.46$, $p < .05$. Simple interaction effect: Size of possible gains × Size of possible losses in participants treated with tryptophan supplements: $F(1, 26) = 61.4$, $p < .05$.

$F < 1.00$]. Similarly, deliberation times were unchanged when the ''experimental'' gamble was associated with large compared to small losses [2731 ± 198 vs. 2725 ± 159 msec; $F < 1.00$]. Neither of these patterns were altered following tryptophan treatment compared to placebo treatment (see Table 4) [$F(1, 26)$s < 2.45].

Overall, participants who were treated with tryptophan showed significantly longer deliberation times when deciding between gambles than those participants who were treated with placebo [3307 ± 288 vs. 2149 ± 179 msec; $F(1, 26) = 11.68$, $p < .005$].

Choice as a Function of Expected Value

Proportionate Choice

Both those participants who received the tryptophan treatment and those who received the placebo treatment chose the ''experimental'' gamble more frequently as its expected value increased from a minimum of −30 to a maximum of +30 (see Table 1) [$F(7, 182) = 64.29$, $p < 0001$]. However, those participants who received tryptophan chose the ''experimental'' gamble significantly more often than those who received placebo only when its expected value was −6 [$F(1, 26) = 8.23$, $p < .01$], and not when its expected value was either higher or lower than this value (see Table 1) [all Fs(1, 26) < 1.88]. [The two-way interaction between treatment and the expected values of all eight gambles did not reach significance, $F(7, 182) = 1.58$.].

Models of Nonnormative Risky Choice: The Reflection Effect

Proportionate Choice

Overall, participants showed the usual reflection effect, that is, they chose the sure gain (of 30 points) over a gamble with a .5 probability of winning a larger gain (60 points) and a .5 probability of winning nothing (''gains-only'' trials) more frequently than they chose the certain loss (of 30 points) over a gamble with a .5 chance of losing nothing and a .5 probability of losing a larger amount (60 points) (''losses-only'' trials) [0.77 ± 0.05 vs. 0.22 ± 0.04; $F(1, 26) = 68.69$, $p < .001$]. However, the size of this preference reversal was significantly attenuated following tryptophan compared to placebo (see Figure 3A) [$F(1, 26) = 11.73$, $p < .005$]. Analysis of

Table 4. Mean Deliberation Times as a Function of High vs. Small Probability of Winning, Large vs. Small Possible Gains, and Large vs. Small Possible Losses

	Probability of Winning		*Size of Possible Gains*		*Size of Possible Losses*	
Group	*High*	*Low*	*Large*	*Small*	*Large*	*Small*
Placebo	2040 ± 190	2264 ± 251	2101 ± 230	2202 ± 211	2130 ± 200	2173 ± 241
Tryptophan	3243 ± 354	3403 ± 387	3425 ± 394	3221 ± 347	3354 ± 413	3292 ± 328

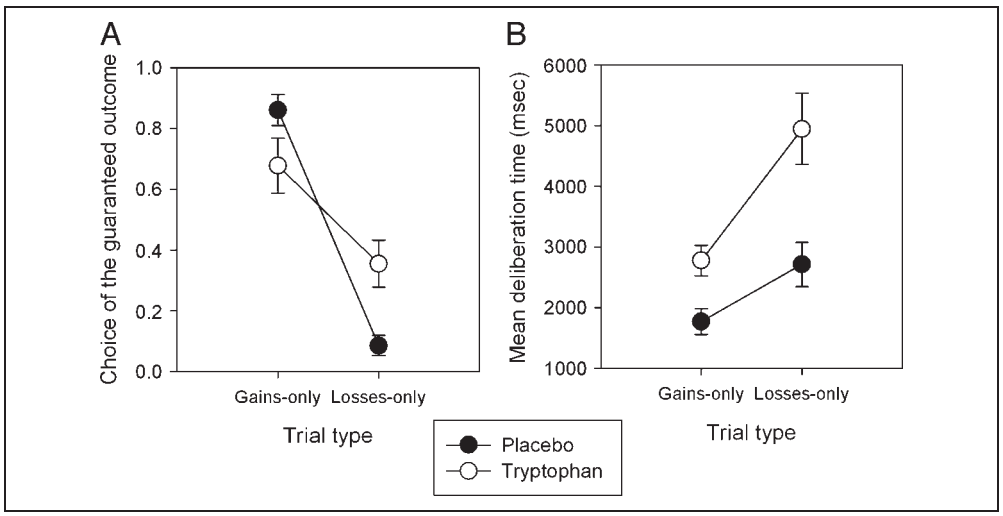

Figure 3. Nonnormative risky choice (the ''reflection effect'') following treatment with tryptophan (3 daily supplements of 1 g) for 14 days (n = 15 participants) and treatment with placebo (n = 15 participants). ''Gains-only'' trials offered a choice between a certain gain of 30 points and a gamble with a .50 probability of winning 60 points or 0 points; ''Losses-only'' trials offered a choice between a certain loss of 30 points or a gamble with a .50 probability of losing 60 points or 0 points. (A) Choice of the guaranteed outcome; Treatment (placebo vs. tryptophan) × Trial type (gains-only vs. losses-only): $F(1, 26) = 11.73$, $p < .005$; simple effect: treatment on losses-only trials: $F(1, 26) = 10.25$, $p < .005$. (B) Mean deliberation times (msec).

the simple effects showed that participants who received tryptophan supplements chose the sure loss on the ''losses-only'' trials significantly more often than participants who received placebo [$F(1, 26) = 10.25, p < .005$].

Deliberation Times

Overall, participants took significantly longer to choose between the certain loss and the gamble with a .5 probability of losing nothing or losing a larger amount (''losses-only'' trials) compared to choosing between a sure gain and a gamble with a .5 probability of winning a larger amount or winning nothing (''gains-only'' trials) [3830 ± 345 vs. 2273 ± 166 msec; $F(1, 26) = 22.96$, $p < .0001$]. There was a tendency for these prolonged decision times to be further increased in those participants who received tryptophan supplements compared to those participants who received the placebo treatment, reflected in a near-significant two-way interaction between treatment and trial type (see Figure 3B) [$F(1, 25) = 3.56$, $p = .07$].

Finally, male participants exhibited a larger increase in deliberation times on the losses only trials relative to the gains only trials (4574 ± 504 vs. 2135 ± 243 msec) compared to female participants (3086 ± 472 vs. 2231 ± 227 msec) [$F(1, 26) = 4.67$, $p < .05$]. No other main effects or interactions were statistically significant.

DISCUSSION

These data indicate that 14 days of treatment with the serotonin precursor, tryptophan, alter the processing of reinforcement signals during risky decision-making and suggest that serotonin activity plays a role in modulating the nonnormative features of decision-making under conditions of uncertainty. These changes in participants' decision-making were not associated with marked changes in subjective state. State anxiety, as well as state positive and state negative affect, showed only marginal changes between baseline and the end of the 14-day treatment in the two groups of study participants. Crucially, there were no significant differences in subjective state between those participants who received tryptophan and those who received placebo at the time point when they completed our risky decision-making task.

This aspect of the data bears comparison with those from an earlier report involving a sample of adult volunteers that overlapped with that of the present experiment (Murphy et al., 2006). In that experiment, the same 14-day treatment with tryptophan supplements did not alter participants' subjective state but instead facilitated the recognition of happy facial expressions and impaired the recognition of disgusted facial expressions. Tryptophan supplements also reduced attentional vigilance toward negative words and baseline startle responsivity in female but not in male adult volunteers. These effects suggest that enhancing serotonin activity by these means reduces sensitivity to negatively valenced information (Harmer, Shelley, Cowen, & Goodwin, 2004) and highlights serotonin's hypothesized role in coping and its resilience to stressful events (Graeff, Guimaraes, De Andrade, & Deakin, 1996). The present risky choice data add to this picture by demonstrating that serotonin activity produces complementary alterations in the way

that individuals combine information about affect-laden cues—both positive and negative—and shifts between risk-averse and risk-seeking actions associated with uncertain outcomes.

The present results contrast somewhat with those of an earlier experiment in which we used investigated the effects of tryptophan depletion—leading to reduced central serotonin activity (Moore et al., 2000)—on performance of the same risky choice task (Rogers et al., 2003). In that experiment, tryptophan depletion significantly diminished healthy adults' discriminations between large and small gains when making risky choices compared to the control procedure. Also, tryptophan depletion did not significantly alter choices of the reflection effect. Consequently, the prediction that tryptophan supplements should increase discrimination between large and small gains is not confirmed by the data presented here, although these data do indicate that tryptophan supplements, increasing serotonin activity, can influence the way in which people combine information about gains and losses when making risky decisions.

However, the version of the task introduced in Rogers et al. (2003) differed in several important respects from the one used here. Specifically, the difference between high and low probabilities was greater in the earlier task compared to the present version (.75 vs. .25 compared to .60 vs. .40), as were the differences between large and small gains and between large and small losses (80 vs. 20 versus 70 vs. 30). As a result, participants' choices with the earlier version of the task showed less variability than in this later version and, potentially, less sensitivity to pharmacological challenge (Rogers et al., 2003). Indeed, confirmation of the greater sensitivity of our revised version of the risky choice task is provided by a recent experiment in which we have found that tryptophan depletion *increased* the reflection effect in healthy adult volunteers (Campbell-Meiklejohn et al., unpublished data).

Rational choice models of how people decide between actions associated with outcomes that have defined values and probabilities of occurrence posit that decision-makers ought, and to some degree do, choose options with the maximal expected value; that is, decision-makers tend to choose actions with the highest aggregate return over a sequence of such choices (Goldstein & Hogarth, 1997; von Winterfeldt & Edwards, 1986). These data show that a 14-day course of the serotonin precursor, tryptophan, modifies such behavior in healthy adults in two distinct ways. Therefore, our results suggest that serotonin activity plays an important role in modulating the apparent rationality of human decision-making under conditions of uncertainty.

First, maximizing expected value implies that, averaged over varying probabilities, choice of actions will reflect the sum of both their good and their bad consequences. Participants who received placebo exhibited just such a rational set of selections. Large possible gains increased their preference for the ''experimental'' gamble compared to small gains, whereas large losses decreased their preference compared to small losses. However, these effects were statistically independent or additive to each other (Figure 2A). This suggests that, confronted with choices between actions associated with large and small gains, and large and small losses, participants who received placebo decided broadly on the basis of their aggregated value.

By contrast, participants who received tryptophan showed quite a different pattern of risky decision-making. Although large possible gains also increased choice of the ''experimental'' over the control gamble compared to small gains, and large losses decreased choice of the ''experimental'' gamble compared to small losses, these effects were not now statistically independent of one another. Rather, participants who received tryptophan supplements showed more frequent choice of the ''experimental'' gamble when it was associated with both small gains *and* small losses (Figure 2B), indicating that their selections did not reflect the aggregated value of gains and losses but, instead, a multiplicative combination of good and bad outcomes.

At the current time, it is unclear why tryptophan should have altered the way in which healthy adults combine information about gains and losses when making risky choices. However, one important clue may be the relative pattern of choices of the ''experimental'' gamble made by the treatment groups as a function of expected value (Table 1). Both the participants who received tryptophan and those who received placebo showed a greater preference for the ''experimental'' gamble over the control gamble as its expected value increased from negative into positive values. However, tryptophan was associated with significantly more frequent choices of the ''experimental'' gamble, compared to placebo, when its expected value was −6, but not when its expected value was either greater or smaller than this value.

Our finding that tryptophan increased choices of gambles with small, negative expected values was not predicted and requires further exploration and replication. However, empirical research and theories of decision-making under conditions of risk have noted that small prospective losses can substantially impact on peoples' choices (compared, say, to small gains), sometimes producing patterns of loss-averse behavior (Khaneman & Tversky, 1979). Our data suggest that tryptophan treatment—leading to an increase in serotonin activity—reduces the impact of small losses when deciding between actions associated with uncertain outcomes or, alternatively, reduces decision-makers' ability to distinguish between options or ''prospects,'' with low or modest negative expected values. These findings are also consistent with suggestions that serotonin activity influences preference for *small*, immediate rewards over larger, delayed rewards through its modulatory action over circuits

incorporating ventral and dorsal sectors of the striatum, respectively (Tanaka et al., 2007).

More information about the role of serotonin on risky choice is provided by examining how our two groups of participants reacted to choices that were included to explore the ''reflection effect.'' Typically, when confronted with a choice between a guaranteed gain and an opportunity to play a gamble with an equal chance of winning a larger gain still or winning nothing at all, decision-makers readily opt for the risk-averse option and take the certain gain. By contrast, when confronted with a choice between a guaranteed loss and the opportunity to play a gamble with a chance of suffering a larger loss still or no loss at all, decision-makers opt for the risk-seeking option and play the gamble (Shafir & Tversky, 1995). Because the expected values associated with the two alternatives in our ''gains-only'' and ''losses-only'' trials were equal, and rational decision-makers in the business of maximizing expected value should have been indifferent between them, the reflection effect exemplified by the participants who received placebo (see Figure 3A) constitutes good evidence that decision-making under conditions of uncertainty is not wholly normative or rational.

Descriptive accounts attribute the reflection effect to the ways that gains and losses, relative to a current reference point, relate to changes in subjective value or utility (Khaneman & Tversky, 1979). Specifically, the concave function between actual gains and increased utility favour risk-averse selections between a certain gain and a 50/50 gamble to win twice that gain or no gain at all, while the convex function between real losses and diminished utility favour risky choice selections between a certain loss and a 50/50 gamble offering twice that loss or no loss at all. Our data indicate that a 14-day course of tryptophan significantly attenuated the ''reflection effect''. Analysis of the simple effects showed that the tryptophan reduced the tendency to gamble to avoid a certain loss at the risk of a greater loss still. Using an earlier version of our risky choice task involving different probabilities, and different magnitudes of gains and losses, we found a comparable pattern of choices associated with the *ll*-allele and *ls*-allele variants of the serotonin transporter gene-linked polymorphic region, 5-HTTLPR, compared to the *s*-allele (Roiser, Rogers, Cook, & Sahakian, 2006). Although the relationship between genotypic variation in 5-HTTLPR and underlying serotonin pre- and post-synaptic activity is likely to be highly complex (David et al., 2005; Smith et al., 2004; Reist, Mazzanti, Vu, Tran, & Goldman, 2001), Roiser et al. (2006) data, together with the results of the present experiment, strengthen our hypothesis that shifts between risk-averse and risk-seeking action selections is influenced by central serotonergic mechanisms.

Of course, several important issues require further investigation. Tom et al. (2007) report that loss-aversion is associated with increased activity in response to larger gains in neural regions that code positive outcomes—specifically, the ventromedial prefrontal cortex, the anterior insula cortex, and the ventral striatum—and decreased activity within the same circuitry in response to greater losses. It may be that the reflection effect arises specifically through serotonergic modulation of reinforcement processes subserved by sites within mesolimbic and mesocortical neural circuits (Walsh & Cunningham, 1997; Aronson et al., 1995). Alternatively, the risk-averse and risk-seeking decision-making exemplified by the reflection effect may also be mediated by serotonergic actions at other sites more directly associated with the processing of aversive signals, and associated anxiogenic states, including the insula and the amygdala (Harmer, Mackay, Reid, Cowen, & Goodwin, 2006).

One limitation of the present experiment is that we did not measure plasma tryptophan levels. The dose used (3 g/day) has previously been demonstrated to increase both plasma and cerebrospinal fluid levels of tryptophan (Young & Gauthier, 1981), suggesting that the tryptophan treatment is likely to have increased central levels of tryptophan. Furthermore, the presence of significant treatment effects on the risky decision-making and the reflection effect, and on a number of other measures of emotional processing reported elsewhere (see Murphy et al., 2006), suggests good compliance with the treatment. However, it would be useful to include plasma tryptophan measurements in future experiments in order to allow the correlation of the biological effects of the tryptophan supplements with risky choices.

To our knowledge, this is the first demonstration that manipulation of a neurotransmitter influences nonnormative aspects of decision-making under conditions of uncertainty. We have shown that treatment with the serotonin precursor, tryptophan, can alter the way human decision-makers combine information about possible gains and possible losses when making risky choices, and can ameliorate the non-normative shifts between risk-aversion and risk-seeking behavior sometimes seen in human risky decision-making. We conclude that serotonin plays a significant role in value-based decision-making.

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Note

1. The NART scores for one participant who received the placebo treatment and one participant who received tryptophan supplements were not available.

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