

Rapid Tryptophan Depletion Improves Decision-Making Cognition in Healthy Humans without Affecting Reversal Learning or Set Shifting

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Rapid tryptophan (Trp) depletion (RTD) has been reported to cause deterioration in the quality of decision making and impaired reversal learning, while leaving attentional set shifting relatively unimpaired. These findings have been attributed to a more powerful neuromodulatory effect of reduced 5-HT on ventral prefrontal cortex (PFC) than on dorsolateral PFC. In view of the limited number of reports, the aim of this study was to independently replicate these findings using the same test paradigms. Healthy human subjects without a personal or family history of affective disorder were assessed using a computerized decision making/gambling task and the CANTAB ID/ED attentional set-shifting task under Trp-depleted ($n = 17$; nine males and eight females) or control ($n = 15$; seven males and eight females) conditions, in a double-blind, randomized, parallel-group design. There was no significant effect of RTD on set shifting, reversal learning, risk taking, impulsivity, or subjective mood. However, RTD significantly altered decision making such that depleted subjects chose the more likely of two possible outcomes significantly more often than controls. This is in direct contrast to the previous report that subjects chose the more likely outcome significantly less often following RTD. In the terminology of that report, our result may be interpreted as improvement in the quality of decision making following RTD. This contrast between studies highlights the variability in the cognitive effects of RTD between apparently similar groups of healthy subjects, and suggests the need for future RTD studies to control for a range of personality, family history, and genetic factors that may be associated with 5-HT function.

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INTRODUCTION

Rapid tryptophan depletion (RTD) is a research technique for transiently reducing brain serotonin (5-hydroxytryptamine (5-HT)) by the ingestion of an excess of large neutral amino acids in the absence of tryptophan (Trp), the precursor of 5-HT. In healthy humans, RTD alters a number of cognitive processes (Riedel, 2004). Most consistently affected are the encoding or consolidation of new information into long-term memory, attentional tasks requiring the suppression of interference from a competing stimulus dimension (eg Stroop Color Word interference task), decision making, and reversal learning. The current study attempts to extend what is known about the effects of RTD on decision making and reversal learning.

Decision making may be defined as the ability to select an advantageous response from a range of available options. Effective decision making requires the integrity of orbito-frontal cortex (OFC) and anterior cingulate cortex (ACC) (Cohen *et al*, 2005), as well as associated subcortical circuitry including the basal ganglia (Krawczyk, 2002) and amygdala (Bechara *et al*, 2003). The OFC may be particularly critical in decisions involving reward and punishment, including gambling. Of particular relevance to this paper, Rogers *et al* (1999b), using a novel computerized decision making/gambling task, found that patients with OFC lesions showed poorer quality decision making with a marked tendency to choose the less likely of two possible outcomes. This impairment was not found in patients with other prefrontal lesions that spared the OFC. A similar deficit was found in two groups of subjects expected to have impaired brain 5-HT levels (chronic amphetamine abusers, and healthy controls following RTD), suggesting that impaired decision making across these groups may be attributed to an hypothesized common deficit in OFC 5-HT. This supports other evidence for an important role for 5-HT in normal decision making. For example, improvement has been reported following acute administration of a selective

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serotonin reuptake inhibitor, while impairment has followed cyproheptadine, a drug with 5-HT_{2A/2C} receptor antagonism (Bechara *et al*, 2001). In addition, RTD impairs the ability to discriminate between differences in the magnitude of rewards associated with different choices (Rogers *et al*, 2003).

Reversal learning refers to the reversal of a previously learned object discrimination, and requires the successful inhibition of a previously conditioned response. Performance on complex cognitive tasks such as the Wisconsin Card Sorting Test (WCST) and several versions of the related Intra/Extra Dimensional Attentional Set Shifting task (ID/ED task), suggests that RTD may impair reversal learning while leaving set shifting relatively unimpaired (Park *et al*, 1994; Rogers *et al*, 1999a). Set shifting is particularly associated with activation of dorsolateral prefrontal cortex (DLPFC) (see eg, Nagahama *et al*, 2001). In contrast, activations associated with reversal learning have been found in ventrolateral PFC (VLPFC) (Cools *et al*, 2002; Nagahama *et al*, 2001) and ventral caudate nucleus (Rogers *et al*, 2000). Studies in monkeys suggest that deficits in reversal learning following lesions of the OFC involve a failure to suppress the influence of previously learned stimulus–reward associations, rather than an impairment in learning new ones (Dias *et al*, 1996). A similar pattern of impaired reversal learning with unimpaired ED set shifting is found following selective 5-HT depletion in the monkey PFC (Clarke *et al*, 2004; Clarke *et al*, 2005). Thus, the association of ventral PFC with reversal learning, and the relatively greater sensitivity of reversal learning to RTD compared to ID or ED set shifting, has suggested that 5-HT may have a more powerful neuromodulatory influence over the VLPFC/OFC-limbic circuitry associated with this kind of learning, rather than the DLPFC circuitry associated with attentional set shifting.

However, the literature on the effects of RTD in humans has a number of limitations. Impairment in decision making secondary to RTD has not been replicated using the same decision making/gambling task, and at least one study has failed to find impaired reversal learning (Murphy *et al*, 2002). With set shifting, some studies have found no impairment (Gallagher *et al*, 2003; Hughes *et al*, 2003), while others have found impaired performance only on the ED shift (Park *et al*, 1994) or the ID shift (Rogers *et al*, 1999a). Therefore, this study aimed to independently replicate the effects of RTD on decision making, reversal learning and set shifting in healthy humans, using the same decision making/gambling task reported by Rogers *et al* (1999b), and the ID/ED task from the computerized Cambridge Neuropsychological Test Automated Battery (CANTAB). In line with the studies summarized above, our hypotheses were that RTD would impair the quality of decision making without inducing risk-taking or impulsive behavior, and would selectively impair reversal learning in comparison with set shifting.

METHODS

Subjects

The study was approved by the local research ethics committee, and all subjects gave informed consent. In all,

32 healthy volunteers (16 males, 16 females) aged 18–60 years participated in a double-blind, randomized, age- and gender-matched, parallel-group study. Participants were allocated to two independent groups (control and RTD), with 16 subjects (eight males and eight females) per group. A crossover design was avoided as the Rogers Decision-Gamble task and the CANTAB ID/ED task are subject to practice effects. Exclusion criteria included: previous experience of the cognitive tests used in this study; any history of psychiatric or neurological morbidity, head injury or substance abuse; a history of affective disorder or schizophrenia in a first-degree relative; hormonal contraception or pregnancy. All premenopausal female subjects were tested during the first 8 days of their menstrual cycle.

Decision-Gamble Task

The task is described in detail by Rogers *et al* (1999b). Briefly, on each trial subjects view a row of 10 red or blue boxes displayed on a computer screen and are told that a yellow token is hidden inside one of them. First, subjects must choose whether they think the token is in a red or blue box. The likelihood of their color choice being correct is indicated by the proportion of red and blue boxes displayed, which is varied across trials (6:4, 7:3, 8:2, 9:1). Having made their color choice, subjects must then decide how many of their points they wish to gamble on being correct. A succession of five possible bets is shown, and subjects are required to select the bet of their choice. Following each bet, the token is revealed. A correct color choice is rewarded by the total of points gambled, whereas a losing choice forfeits that number of points. The task is performed in two separate conditions, the presentation of which is controlled for order effects. In one condition (ascending) the first bet offered is small (5% of the current total points score) and is increased incrementally (25%, 50%, 75%, 95%) until the subject makes a selection. In the second condition (descending) this order is reversed.

The five principal measures in this task are: (i) *Speed of decision making*: the mean deliberation times for choosing 'red' or 'blue'; (ii) *Quality of decision making*: the proportion of trials on which the subject chooses the more likely outcome (ie the color with the greater number of boxes) (iii) *Risk taking*: the mean proportion of available points that a subject bets on each trial; (iv) *Delay aversion*: the difference in risk taking scores between the descending and ascending conditions; (v) *Risk adjustment*: the degree to which a subject increases or decreases the size of their bets in response to more and less favorable ratios of red:blue boxes (eg nine red:one blue *vs* four red:six blue). These measures are described in more detail elsewhere (eg Deakin *et al*, 2004).

ID/ED Attentional Set-Shifting Task

The ID/ED task is a set of visual discrimination and reversal tests that examine a subject's ability to attend to the specific attributes of simple (one-dimension) and compound (two-dimension) stimuli and to shift that attention when required. It was performed on the touch screen CANTAB

V2. System (Sahakian and Owen, 1992). The two dimensions used are color-filled shapes and white lines. In Stage 1, the subject is presented with two shapes and must learn which of them is always correct (simple discrimination). The other dimension (lines) is then added which the subject must learn is irrelevant (Stages 3 and 4; two compound discrimination stages). Completely new examples of the dimensions are then introduced, and the subject must learn that one of the new shapes (ie same dimension) is always correct (Stage 6; ID shift). Shapes then become irrelevant, requiring the subject to attend to the previously suppressed dimension (lines) and learn which of the lines is correct (Stage 8; ED shift). In addition, after each of the above stages, a reversal learning test is interposed. In these stages, the test stimuli and the relevant stimulus dimension of the immediately preceding discrimination are unchanged but the correct exemplar of the dimension is swapped without warning (Stages 2, 5, 7, and 9; reversal).

Study Procedure

Subjects abstained from drinks containing alcohol or caffeine for 24 h prior to the study, observed a low-protein diet on the evening before, and fasted from midnight. Males were given a 104.5 g amino-acid mixture to drink either with (T+; control group) or without (T−; RTD group) Trp in it. The T+ drink contained L-Trp 2.2 g and 15 other amino acids as previously described (Talbot *et al*, 2005). Female subjects received 83.5 g of the same mixtures. Subjects relaxed or read in a quiet room under the supervision of study personnel until cognitive testing started 5 h later, in the following order: (i) Rogers Decision-Gamble task with bets presented in either ascending or descending order; (ii) the CANTAB ID/ED task; (iii) Decision-Gamble task with bets presented in the order opposite to the first presentation. The order in which subjects tackled the two parts of the Rogers Decision-Gamble task was balanced across both genders and amino-acid groups. Before drinking their allocated mixture and before cognitive testing, subjects rated their mood on a 100 mm Happy–Sad visual analogue mood scale (VAMS) and blood was drawn for free and total plasma Trp assay. Verbal IQ was estimated using the National Adult Reading Test (NART) (Nelson, 1982). In order to prevent possible confounding effects of nicotine withdrawal, smokers were permitted to smoke one or two cigarettes during the day, but had to abstain from at least 1 h before the start of cognitive testing.

Statistical Analysis

Data were analyzed using SPSS for Mac OSX version 11.0 (Chicago: SPSS Inc.). Results are expressed as mean \pm SEM. Confidence intervals (CI) are 95%, computed using $\alpha = 0.05$. Estimates of effect size are partial Eta-squared values (hp^2), where hp^2 is the proportion of the effect plus error variance that is attributable to the effect. Socio-demographic variables, baseline VAMS score, and baseline total and free Trp levels were compared between groups by unpaired *t*-test. Changes in VAMS score and total and free Trp levels across time points were analyzed by repeated measures (RM) ANOVA, with group (T+ or T−) as between-subjects factor. Frequency data (certain socio-demographic factors and 'stage reached' on ID/ED task) were analyzed using the χ^2 test. Variables from the Decision-Gamble task were analyzed by RM ANOVA as described by Rogers *et al* (1999b), with group, gender and order of condition (ascending/descending *vs* descending/ascending) as between-subjects factors. Condition (ascending *vs* descending bet presentation), decision (red *vs* blue), and ratio (6:4 *vs* 7:3 *vs* 8:2 *vs* 9:1) were within-subjects factors. Deliberation times from the ID/ED task were analyzed by RM ANOVA, with group and gender as between-subjects factors and mean deliberation times across stages as within-subject factor. Scores for errors and stages were analyzed by Mann–Whitney *U* test, as the data did not conform to normality and homogeneity of variance requirements for parametric analysis, even after transformations were applied. However, as previous studies have used parametric analysis (Park *et al*, 1994; Rogers *et al*, 1999a), we also analyzed the data by RM ANOVA for comparison, with group (T− *vs* T+) as between-subjects factor and stage as within-subjects factor.

RESULTS

Participants

One male subject inadvertently received a T− rather than a T+ mixture. Thus, the final T− and T+ groups comprised 17 and 15 subjects, respectively. Nine of the male subjects (four T− and five T+) had previously received both amino-acid mixtures (in a blinded fashion) in another RTD study (Talbot and Cooper, 2004). Subject characteristics and mean Trp concentrations are shown in Table 1. Treatment groups were well matched for age ($t(30) = -0.25$, $p = 0.81$), gender ($\chi^2(1) = 0.13$, $p = 0.72$) and verbal IQ ($t(28) = -1.48$,

Table 1 Characteristics of Control (T+) and RTD (T−) Groups

Group	Number	Gender (M/F)	Age (years)	NART	Total Trp ($\mu\text{g/ml}$)		Free Trp ($\mu\text{g/ml}$)	
					Baseline	5 h post	Baseline	5 h post
T+	15	7/8	33.9 \pm 2.6	117.0 \pm 1.7	12.83 \pm 1.48	22.72 \pm 1.66	0.69 \pm 0.12	1.15 \pm 0.10
T−	17	9/8	34.7 \pm 2.3	113.5 \pm 1.7	14.50 \pm 1.39	2.79 \pm 1.55*	0.56 \pm 0.11	0.16 \pm 0.09*

NART: National Adult Reading Test; Trp: tryptophan.

Values are mean \pm 1 SE.

*Significantly different from T+ condition ($p < 0.001$).

$p=0.15$). None of the T⁻ subjects, and four of the T⁺ subjects, were smokers (approximate number of cigarettes smoked daily = 3, 5, 10, and 20, respectively).

Plasma Trp and Mood

The T⁻ and T⁺ groups did not differ significantly in baseline plasma total Trp ($t(29) = -0.76$, $p = 0.45$) or free Trp ($t(29) = 0.83$, $p = 0.41$) levels (Table 1). At 5 h, plasma Trp levels were significantly reduced in the T⁻ group when compared to the T⁺ group (Total Trp*Group interaction: $F(1,28) = 49.86$, $p < 0.001$, $hp^2 = 0.640$; Free Trp*Group interaction: $F(1,28) = 25.12$, $p < 0.001$, $hp^2 = 0.473$). In the T⁻ group, the mean reductions in total and free plasma Trp concentrations were 79.6 and 65.8%, respectively. In the T⁺ group, the mean increases in total and free plasma Trp concentrations were 83.6 and 121.3%, respectively.

The groups did not differ significantly in baseline 'Happy-Sad' VAMS scores ($t(30) = 0.56$, $p = 0.58$). At 5 h, there was no significant VAMS score*Group interaction ($F(1,30) = 0.07$, $p = 0.79$, $hp^2 = 0.002$), indicating that there was no selective effect of RTD on subjective mood.

Speed of Decision Making

Mean deliberation time for the T⁻ group was 1974 ± 113 ms (CI: lower bound = 1733 ms, upper bound = 2216 ms) and for the T⁺ group was 2130 ± 137 ms (CI: lower bound = 1836 ms, upper bound = 2425 ms). The difference between groups was not significant (main effect of Group: $F(1,30) = 0.66$, $p = 0.42$; $hp^2 = 0.022$). Although deliberation times differed significantly across the ratios of colored boxes (main effect of Ratio: $F(3,90) = 17.83$, $p < 0.001$; $hp^2 = 0.373$), there was no significant Group*Ratio interaction ($F(3,90) = 1.42$, $p = 0.24$; $hp^2 = 0.045$), indicating that amino-acid allocation did not differentially affect decision-making times across the ratios of colored boxes. All other main effects and two-way interactions, including gender effects, were nonsignificant.

Quality of Decision Making

The T⁻ group chose the more likely of the two available outcomes $98.7 \pm 0.6\%$ of the time (CI: lower bound = 97.3%, upper bound = 100.1%), while the T⁺ group chose the more likely of the two available outcomes $92.2 \pm 1.8\%$ of the time (CI: lower bound = 88.4%, upper bound = 96.0%) (see Figure 1). This difference between groups was highly significant (main effect of Group: $F(1,30) = 13.54$, $p = 0.001$; $hp^2 = 0.311$), indicating that the T⁻ group chose the more likely of the two available outcomes significantly more often than the T⁺ group. The effect of amino-acid allocation on the quality of decision making was similar across the ratios of colored boxes (Group*Ratio interaction: $F(3,90) = 1.03$, $p = 0.38$; $hp^2 = 0.033$). All other main effects and two-way interactions, including gender effects, were nonsignificant.

Risk Taking, Delay Aversion and Risk Adjustment

The mean proportion of available credit bet by the T⁻ group was $51.0 \pm 3.1\%$ (CI: lower bound = 44.7%, upper bound = 57.3%), while for the T⁺ group it was $44.4 \pm 2.6\%$

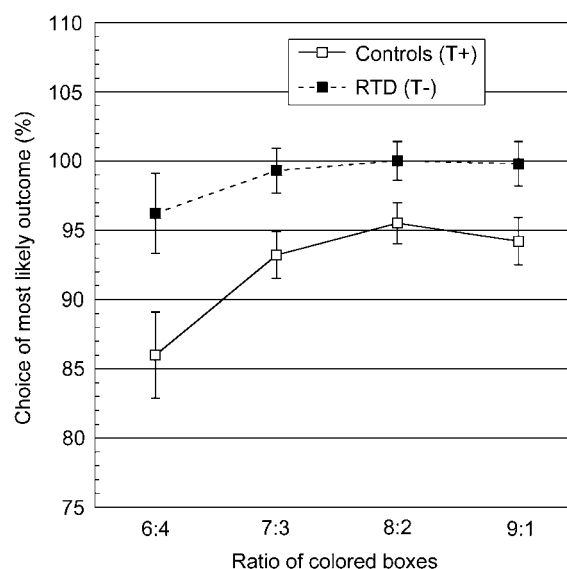


Figure 1 Quality of decision making. Percentage of choice of the more likely outcome, as a function of the ratio of red and blue boxes. Error bars represent 1 SEM. Tryptophan depleted (T⁻) subjects chose the more likely outcome significantly more often than controls (T⁺), $p = 0.001$.

(CI: lower bound = 39.0%, upper bound = 49.8%). This difference in risk taking between groups was not significant (main effect of Group: $F(1,30) = 1.58$, $p = 0.22$; $hp^2 = 0.050$). Bets were significantly smaller in the ascending condition than the descending condition (ascending: $44.4 \pm 2.6\%$ (CI: lower bound = 39.0%, upper bound = 49.8%), descending: $53.1 \pm 2.6\%$ (CI: lower bound = 47.8%, upper bound = 58.4%); $F(1,30) = 8.94$, $p = 0.006$; $hp^2 = 0.230$). However, this effect of presentation order on the choice of bet size did not differ between groups (Group*Condition interaction: $F(1,30) = 0.024$, $p = 0.88$; $hp^2 = 0.001$). The percentage of points risked differed significantly across the ratios of colored boxes (main effect of Ratio ($F(1.4,40.7) = 77.23$, $p < 0.001$; $hp^2 = 0.720$). However, there was no difference in risk adjustment between groups (Group*Ratio interaction: $F(3,90) = 0.33$, $p = 0.80$; $hp^2 = 0.011$). All other main effects and two-way interactions were nonsignificant.

CANTAB: ID/ED Attentional Set-Shifting Task

All participants reached at least Stage 7 (ID reversal). The T⁻ group did not significantly differ from the T⁺ group in the number of subjects who reached Stage 9 (final stage; ED reversal) (Stage 7 or 9: $\chi^2(1) = 0.74$, $p = 0.39$), the total number of trials completed ($U(15,17) = 100.5$, $p = 0.31$) or the number of errors made ($U(15,17) = 111.0$, $p = 0.53$) on this test (Figure 2). Errors at the reversal learning stages of the task did not differ between groups (Stage 7 (ID reversal): $U(15,17) = 118.0$, $p = 0.48$; Stage 9 (ED reversal): $U(11,10) = 51.5$, $p = 0.77$). The above measures remained nonsignificant when the secondary parametric analysis was used (data not shown). Mean deliberation time across test stages for the T⁻ group was 2837 ± 128 ms (CI: lower bound = 2575 ms, upper bound = 3100 ms) and for the T⁺ group was 2746 ± 137 ms (CI: lower bound = 2466 ms, upper bound = 3025 ms). These times did not significantly differ between groups (main effect of Group: $F(1,30) = 0.24$,

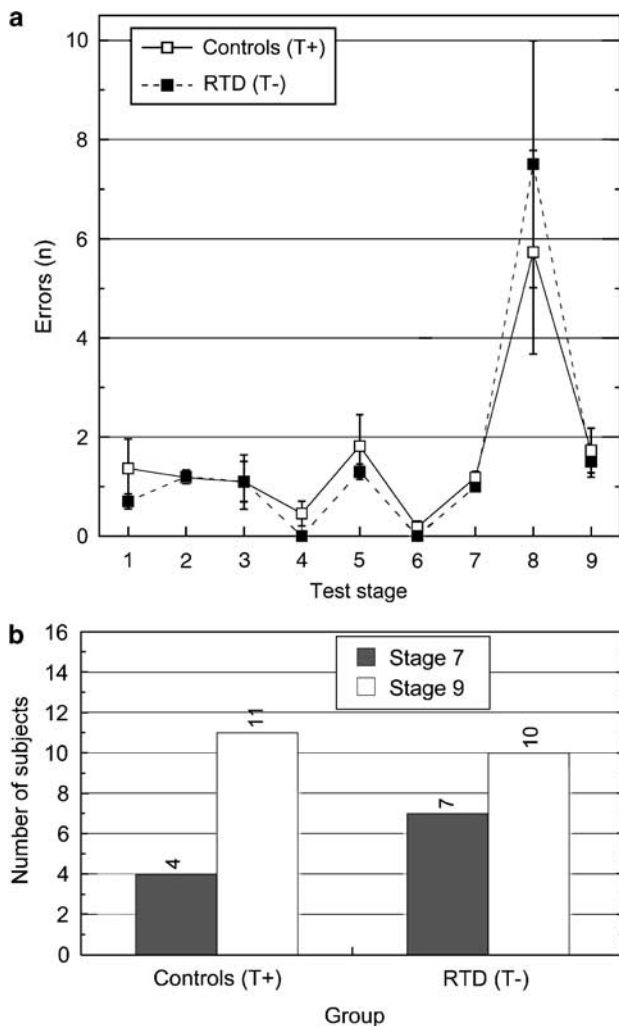


Figure 2 (a) Errors on ID/ED task across test stages. Error bars represent 1 SEM. No significant differences were found between T- and T+ groups. (b) The number of subjects in T- and T+ groups who completed the ID/ED task at Stages 7 (failed) and 9. No significant group differences were found.

$p = 0.63$; $hp^2 = 0.008$). While deliberation times differed significantly across test stages ($F(1.45, 43.62) = 617.48$, $p < 0.001$; $hp^2 = 0.954$), this effect did not significantly differ between groups (Group \times Stage interaction: $F(1.45, 43.62) = 0.75$, $p = 0.44$; $hp^2 = 0.024$).

DISCUSSION

The main finding of the study is that RTD significantly improved the quality of decision making of healthy volunteers as measured by the Rogers Decision-Gamble task. In other words, the RTD group showed a significantly greater tendency to choose the more likely outcome (ie that the token was hidden in a box of the more prevalent color) when compared to the control group, across all ratios of red to blue boxes (see Figure 1). No significant differences were found between groups in speed of decision making, risk taking, delay aversion, or risk adjustment. Nor did RTD significantly alter set shifting or reversal learning as measured by the CANTAB ID/ED task.

Our finding that RTD did not alter risk taking or induce impulsive decision making is in agreement with Rogers *et al* (1999b), and supports an emerging consensus that RTD does not alter risk taking in healthy humans (Anderson *et al*, 2003; Rogers *et al*, 2003). In addition, the improvement in quality of decision making is consistent with several other studies demonstrating improvement in cognitive function associated with PFC. In particular, RTD has improved performance on Stroop-like interference tasks in the majority of (Coull *et al*, 1995; Rowley *et al*, 1997; Schmitt *et al*, 2000), but not all (Hughes *et al*, 2003; Sobczak *et al*, 2002), studies that have investigated this. The association of Stroop performance and decision-making cognition with dorsal ACC function may suggest a relatively strong neuromodulatory effect of RTD on this region in these studies. In support of this, we have recently shown that RTD (using identical T+ and T- mixtures to this study) led to a highly significant decrease in regional cerebral blood flow in dorsal ACC (Talbot and Cooper, 2004).

However, the finding of significantly better quality of decision making in the RTD group is directly *opposite* to the results reported by Rogers *et al* (1999b). In that study, using the same Decision-Gamble task in a similar group of healthy volunteers, the RTD group showed a significantly *decreased* tendency to choose the more likely outcome. On the basis of this, RTD was reported to induce a deterioration in the quality of decision making. Moreover, the degree to which the RTD group chose the more likely outcome as a function of the ratio of colored boxes in our study is strikingly similar to the degree to which the control group in the study of Rogers *et al* chose the more likely outcome (see Figure 3c in Rogers *et al*, 1999b). Explanation of this directional difference between studies is necessarily speculative. It may possibly relate to unmeasured intrinsic trait characteristics of the individuals tested, as directionally opposite effects of RTD have previously been reported. For example, while it is generally appreciated that the effects of RTD may differ depending on a personal or family history of affective disorder, there is increasing evidence that RTD can have directionally opposite effects depending on trait characteristics such as aggression (Bjork *et al*, 2000) and genetic factors associated with a family history of alcoholism (Crean *et al*, 2002). Moreover, structure, function and interconnections within the ventral PFC are known to be affected by genetic variation within the 5-HT system (Pezawas *et al*, 2005). It seems reasonable to speculate that the neuromodulatory effects of reduced 5-HT on ventral PFC may also vary according to these genetic differences. As the previously reported impairments in decision making and reversal learning following RTD have been ascribed to a more powerful neuromodulatory effect of altered 5-HT on ventral PFC, our finding that neither of these cognitive functions was impaired may possibly imply significant, genetically determined, variation in the effects of RTD on ventral PFC function between apparently similar groups of healthy subjects. Such factors were not controlled for in these studies. The use of personality inventories, genotyping for key serotonergic polymorphisms, and close attention to family history should permit future studies to more closely match for personality and genetic factors.

Explanations related to measured parameters seem less apparent. The design and demographic characteristics of the studies are very similar, and both groups have rechecked their randomization and analysis (Dr RD Rogers and Professor JFW Deakin, personal communications). In both groups, the number of males and females was the same, subjects with a personal or family history of depression were excluded, subjective mood remained unchanged following RTD, female subjects were studied only in the follicular phase of their menstrual cycle, and cognitive testing began at 5 h. The Trp content of the control drink (2.2 vs 2.3 g), and the reduction in total (by 80 vs 74%) and free (by 66 vs 73%) plasma Trp levels, appear comparable. On the other hand, there are some small methodological and sampling differences between the studies, and it remains possible that these may have contributed to the contradictory findings. For example, our group had a slightly higher mean NART score (115 vs 110) and age (34 vs 28 year), although the effect of such a modest age difference is unlikely to be strong on baseline 'quality of decision making' for the Decision-Gamble task (Deakin *et al*, 2004). Unlike Rogers *et al*, we excluded female subjects taking hormonal contraception in an attempt to minimize confounding hormonal effects on cognitive function. In addition, neural responses to RTD in heavy smokers may not be the same as in other healthy subjects (Pergadia *et al*, 2004), and evidence is accumulating for a modest effect of short-term abstinence on cognitive function, including attention, in smokers (see, eg Cook *et al*, 2003). Our group contained few smokers ($n = 4$; two males and two females), only one of whom might be considered to smoke heavily, and these were permitted to smoke one to two cigarettes during the study day if they felt that it was necessary. Smokers in the Rogers *et al* study (number and consumption unknown) were requested to abstain from midnight before the study day, raising the possibility that the anticipation or experience of withdrawal symptoms in some subjects may have affected cognitive function.

Our results on the CANTAB ID/ED task would broadly support the lack of consistent effect of RTD on dimensional set shifting in previous reports. For reversal learning, while we failed to duplicate the adverse effects of RTD previously described, our negative finding is similar to that of Hughes *et al* (2003). While variability in the neuromodulatory effects of RTD may have contributed to differences between studies, different task versions used may also have contributed. Rogers *et al* (1999a) used a more attentionally demanding (discrimination over three stimulus dimensions rather than two) version of the ID/ED task than the CANTAB version used in this study and the study by Hughes *et al*. However, Park *et al* (1994) used the less demanding CANTAB version and still found that RTD resulted in more errors and an increase in the number of trials needed to reach criterion, particularly on reversal stages. In our study, the large intersubject variability in the scores generated by this particular version may have prevented the detection of group differences in reversal learning. Future studies should therefore use the more demanding version of this task, which is also a closer approximation of the WCST.

In conclusion, we found that RTD significantly improved the quality of decision making of healthy volunteers as measured by the Rogers Decision-Gamble task, without

significantly altering set shifting or reversal learning as measured by the CANTAB ID/ED task. In addition, we found no evidence that RTD significantly increased risk taking or impulsive decision-making behavior. Comparison with previous studies highlights the variability in the effects of RTD between apparently similar groups of healthy subjects, and the need for future studies to control for personality and genetic factors, particularly those related to 5-HT function.

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