Social Cognitive and Affective Neuroscience Advance Access published July 23, 2009

doi:10.1093/scan/nsp025 SCAN (2009) 1 of 12

The effect of acute tryptophan depletion on emotional distraction and subsequent memory

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Serotonin is a key neurotransmitter involved in emotional regulation and memory. A number of studies using acute tryptophan depletion (ATD) in healthy subjects have shown that a temporary serotonin reduction both induces a negative emotional bias and impairs long-term memory. However, little is known about the specific effects of ATD on emotional memory. Using functional magnetic resonance imaging (fMRI), we investigated the effect of ATD on negative memory and executive function in healthy volunteers. Our emotional oddball task required participants to distinguish infrequently presented targets from distracting negative and neutral pictures. Memory for the distracting pictures was tested 1 h following the fMRI session. ATD selectively enhanced memory for negative distractors relative to neutral distractors and increased activation in response to the negative distractors in the left orbital-inferior frontal, dorsomedial prefrontal and bilateral angular gyri. ATD also induced greater activation in the left inferior frontal gyrus and anterior cingulate across all stimuli. Stronger frontal activation to distractors was positively correlated with memory performance on ATD but not control days, indicating a possible compensatory mechanism for coping with increased task demand under the ATD challenge. These findings highlight the importance of serotonin in negative memory with implications for mood disorders.

Keywords: serotonin; emotional memory; negative attentional bias; distraction; fMRI

INTRODUCTION

Serotonin (5-HT) is a key neurotransmitter involved in a variety of behavioral processes such as emotional regulation, memory and executive control. Deficits in serotonergic function have been strongly associated with depression and other psychiatric disorders (Coppen and Wood 1982; Delgado *et al.*, 1990; Meltzer 1990; Owens and Nemeroff 1994). Acute tryptophan depletion (ATD), which temporarily reduces 5-HT synthesis, is a well-established experimental method for studying the effects of transient low 5-HT *in vivo* (Young *et al.*, 1985; Reilly *et al.*, 1997; Bell *et al.*, 2001). Reducing 5-HT levels via ATD has rapid and significant effects on mood and emotional processing, leading to transient depressive symptoms in many individuals remitted from depression (Booij *et al.*, 2002; Neumeister *et al.*, 2004) or with a family history of depression (Sobczak *et al.*, 2002; van der Veen *et al.*, 2007). For healthy volunteers, ATD does not typically cause these depressive symptoms, but has been found to induce changes in performance on tasks related to emotion, memory and cognitive control (Riedel *et al.*, 1999; Schmitt *et al.*, 2000; Sobczak *et al.*, 2002; Evers *et al.*, 2005). Given the increasing interest in using individual differences in the response to ATD as an indicator of serotonergic vulnerability (Booij *et al.*, 2005; Jans *et al.*, 2007), it is important to elucidate the effect of ATD on emotion and cognition in healthy individuals.

A number of recent studies have found that depleting central 5-HT through ATD produces attentional biases toward negative stimuli (Murphy *et al.*, 2002; van der Veen *et al.*, 2007; Roiser *et al.*, 2008), a phenomenon which has been well-documented in the literature of depression and other mood disorders (Lloyd and Lishman, 1975; Clark and Teasdale, 1982; Blaney, 1986; Gotlib and Cane, 1987; Gur *et al.*, 1992; Bradley *et al.*, 1996; Murphy *et al.*, 1999; Gotlib *et al.*, 2004; Surguladze *et al.*, 2004). Murphy and colleagues (2002) reported that ATD increased response time (RT) for happy but not for sad target words in an affective go/no-go task. In a similar affective go/no-go task, Roiser and colleagues (2008) found that participants in the control condition made more incorrect responses to happy distractors than to sad distractors, and that ATD removed this bias for positive stimuli. Evers and colleagues (2006) reported evidence of a negative bias using an affective Stroop task: ATD led to an increased number of errors on color naming for negative words and slower reaction times (RT) for negative than for positive or neutral words. Together, these results suggest that ATD leads to negative attentional biases and are consistent with the stronger claim

Received 17 November 2008; Accepted 21 June 2009

We thank Brandi Newell for manuscript comments. We also thank the staff of the Brain Imaging and Analysis Center and the Duke Clinical Research Unit for technical support. This research was supported by the Duke Silvio O. Conte Center for the Neuroscience of Depression (P50-MH60451). L.W. is supported by the Paul B. Beeson Career Developmental Awards (K23-AG028982).

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that low serotonin plays a central role in the negative biases observed in mood disorders, although conflicting results exist (Harmer *et al.*, 2003).

In addition to evoking a negative attentional bias, ATD also impairs long-term memory formation and memory consolidation (Riedel *et al.*, 1999; Schmitt *et al.*, 2000; Merens *et al.*, 2007; Sambeth *et al.*, 2008). However, little is known specifically regarding the effects of ATD on memory for stimuli with emotional content. Given that ATD tends to increase attention to negative stimuli, an intriguing hypothesis is that ATD might counterintuitively enhance recall of negative events even if memory performance is otherwise impaired. A neuroimaging study that used neutral words as stimuli asked subjects to indicate how pleasant/unpleasant they found each word (van der Veen *et al.*, 2006). The authors did not find impaired memory during a subsequent memory test, but found decreased neural activation in the right hippocampus during encoding. Given that >70% of the stimuli were subjectively rated as 'pleasant' by the subjects, a lack of statistical power may have camouflaged an effect of ATD for negative memory encoding. To our knowledge, there is only one report in the literature that explicitly studied the effect of ATD on emotional memory. Klaassen and colleagues (2002) tested participants' memories for negative, neutral and positive words 6 and 24 h after the ingestion of the tryptophan-depleted drink. ATD preferentially impaired recall of neutral and positive words, while leaving the recall of negative stimuli intact. Since the results did not show enhanced memory for negative stimuli, the question of a negative memory bias remains unanswered. Therefore, it is necessary to further clarify the effects of ATD on the encoding of negative stimuli into memory.

The reported effects of ATD on executive function are varied. Some studies have reported that ATD improved executive function (Schmitt *et al.*, 2000; Murphy *et al.*, 2002; Gallagher *et al.*, 2003; Evers *et al.*, 2006; Scholes *et al.*, 2007), some have shown no effects (Gallagher *et al.*, 2003; Hughes *et al.*, 2003), while others have found no behavioral effects despite ATD-induced changes in brain function. Allen and colleagues found that ATD attenuated activation in the right dorsolateral prefrontal cortex (dlPFC) in a two-back task, even though there were no effects of ATD on task performance (Allen *et al.*, 2006). Horacek and colleagues observed increased activation in bilateral medial frontal cortex, anterior cingulate and left dlPFC during the Stroop task; again, behavioral measures for both tasks remained constant across ATD and control conditions (Horacek *et al.*, 2005). The dlPFC is highly sensitive to serotonergic modulation (Yatham *et al.*, 2001), and dysfunction of this region has been consistently found in depressed patients (Siegle *et al.*, 2006; Steele *et al.*, 2006; Roiser *et al.*, 2008). Clarifying whether low serotonin directly alters the function of the dorsal executive system will deepen our understanding of the neuropathology of depression.

In the current study, we investigated the effect of ATD on attentional bias, emotional memory and executive control. We employed an emotional oddball task to allow us to separately examine the neural processes involved in emotional and executive processing (Yamasaki *et al.*, 2002; Wang *et al.*, 2005) and a subsequent recognition task to examine the successful encoding of negative pictures. While negative memory bias has been associated with increased amygdalar activation in individuals with major depression (Hamilton and Gotlib, 2008), top-down neuroadaptive processes may play a more important role in emotional memory within healthy subjects (Evers *et al.*, 2005; Fusar-Poli *et al.*, 2007; van der Veen *et al.*, 2007; Roiser *et al.*, 2008). Therefore, we hypothesized that the effects of ATD upon negative memory bias would be driven by changes in prefrontal and/or amygdalar activation following the processing of emotionally negative stimuli. We further hypothesized that ATD would decrease activation in the dorsal executive system during the target detection task, but would not change the participants' detection accuracy. Examination of both emotional and executive function allowed us to dissociate regions that are sensitive to the modulation of serotonin, regardless of the task, from those that are selectively sensitive to serotonin during particular cognitive processes.

METHODS

Thirteen healthy volunteers (seven males, mean ± s.d. age = 24.4 ± 3.2 years) participated in the study. Participants were screened by phone and by written questionnaires for history of neurological and psychiatric disorders, drug abuse and current medication use. All participants were screened for current depression using the Zung Self-Rating Depression Scales (scores <34). No participant reported any prior history of depression, other neurologic or psychiatric illness or drug addiction (five participants reported some family history of depression). Data from one participant could not be analyzed due to technical issues, resulting in 12 participants in our reported analyses. All participants provided written informed consent under a protocol approved by the Institutional Review Board at Duke University Medical Center.

Experimental design

In our emotional oddball task (Yamasaki *et al.*, 2002), participants pressed a button with their right index finger when target stimuli appeared (circles) and pressed another button with their middle finger in response to all other stimuli; these nontargets included frequent standards (squares), as well as infrequent distractors (negative and neutral pictures). The pool of emotionally negative and neutral pictures was taken from the International Affective Picture System as well as our previous emotional oddball task (Wang *et al.*, 2006). To avoid habituation effects, all of the distractors were trial-unique pictures within and across

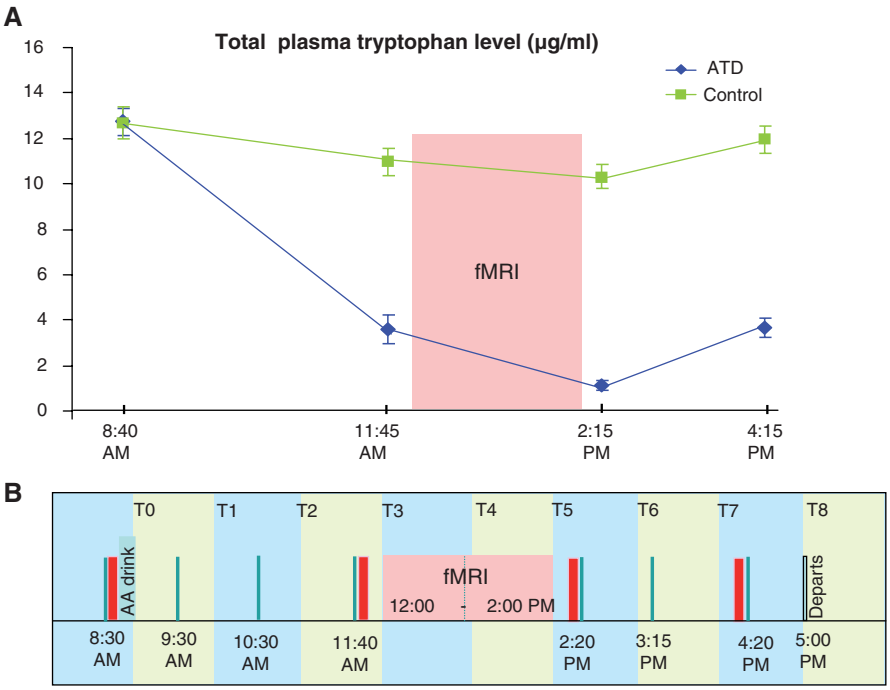

Fig. 1 (**A**) Percentage change of plasma total tryptophan level across time relative to baseline. Peak change was reached at 2:15 p.m. (5.5 hr after the ingestion of the tryptophan-depleted amino acid mixture); (**B**) Time flow of the procedures illustrating the relationship of the blood draw for measuring tryptophan level (red lines) with mood measurements (green lines), amino acid (AA) drink intake and fMRI scan. T0 to T8 indicate time in hours passed after the AA drink intake.

scanning sessions. Across seven runs, the frequency of each type of stimuli was: targets 5.3%, negative distractors 4%, neutral distractors 4% and standards 86.7%. Each stimulus was presented for 1500 ms with an inter-stimulus interval of 2000 ms. The rare stimuli (i.e. targets and distracting pictures) occurred randomly with 14–18 s between successive rare events.

One hour after the end of the scanning session, subjects participated in a rating and recognition task of 84 old and 84 new (42 negative, 42 neutral) images. Subjects were asked to rate the pictures on unpleasantness (1 = Not at All to 5 = Very Unpleasant), arousal (1 = Not at all to 5 = Very Aroused) and recognition (1 = Yes, 2 = Familiar, 3 = No). For the recognition task, the question was: 'Seen it inside the scanner today?' Since a 'Familiar' response has been shown to indicate low confidence and low memory accuracy (Sperling *et al.*, 2003; Schon *et al.*, 2004; Prince *et al.*, 2005; Dennis *et al.*, 2008), we collapsed both 'Familiar' and 'No' responses into the unremembered category in our data analyses.

Procedures

The experiment was conducted in three sessions: one preliminary session and two experimental sessions (ATD and control). The ATD and control sessions were presented in a counterbalanced order (across subjects) with 7–10 days separation. We used an open-label design, in which both the participants and the experimenters knew the identity (ATD or control) of the experimental session at the start of each day. During the preliminary session, participants were screened and trained on the tasks. They were instructed to consume only foods that are low in tryptophan for the 24-h period prior to each experimental day and to fast on the mornings of the experimental sessions. At the start of each experimental session, subjects underwent a dietary recall for this 24-h period; no subjects consumed >500 mg of tryptophan.

For the experimental sessions (Figure 1), participants arrived at the laboratory at 8:30 a.m., where they completed a mood questionnaire and provided a blood sample. On the ATD day, participants then ingested a tryptophan-depleting amino acid drink, while on the control day subjects were given only water. Throughout the remainder of each session, participants regularly completed mood/anxiety questionnaires and underwent blood draws. We assessed levels of emotional valence and arousal using the Self-Assessment Manikin (Lang and Cuthbert, 1999), levels of stress using the Visual Analogue Scale (VAS), levels of mood using the Positive Affect and Negative Affect scale (PANAS) and levels of anxiety using the Spielberger State and Trait Anxiety Inventory (STAI-State). At noon, the subjects participated in a 2-h functional magnetic resonance imaging (fMRI) session that included the emotional oddball task as the final task, which was conducted between ~1:20 and 2:00 p.m.

The tryptophan depletion drink

For seven subjects (three males and four females), the contents of the tryptophan-depleted amino acid mixtures were

the same as described by Young and colleagues(1985). The content of the drink was: 5.5 g L-alanine, 4.9 g L-arginine, 2.7 g L-cysteine, 3.2g L-glycine, 3.2 g L-histidine, 8 g L-isoleucine, 13.5 g L-leucine, 8.9 g L-lysine, 3.0 g methionine, 5.7 g L-phenylalanine, 12.2 g proline, 6.9 g L-serine, 6.9 g L-threonine, 6.9 g L-tyrosine and 8.9 g L-valine. Following some subjects' aversive responses (e.g. nausea and vomiting), we dropped the dosage to 80% of the original drink volume. No vomiting or nausea was reported with the reduced dosage. No significant differences in plasma tryptophan levels were found between the initial seven and later six subjects, suggesting that the 80% dosage is an effective ATD manipulation which allows us to avoid the side-effect of nausea that could potentially alter the subjects' behavior in some tasks.

Biochemical measures

Blood samples (10 ml) were taken to determine plasma amino acid level. The blood was centrifuged and stored frozen at −80°C until analysis. High-performance liquid chromatography was used to determine plasma amino acid concentrations (van Eijk *et al.*, 1994). Below we report the total tryptophan level (a combined measure of protein-bound and free plasma tryptophan). Total tryptophan and free plasma tryptophan are highly correlated and fall comparably after tryptophan depletion, so that total tryptophan provides a validated measure of the effectiveness of tryptophan depletion (Williams *et al.*, 1999).

Image acquisition and analysis

Functional images were acquired using a 3.0-Tesla GE scanner at the Duke-UNC Brain Imaging and Analysis Center. After an initial localizer scan, we acquired two whole-brain structural images, a spoiled gradient-recalled acquisition T_1-weighted image (matrix = 256 × 256 × 180, 1 mm^3) and a T_2-weighted image (matrix = 64 × 64 × 34, 3.8 mm^3), both with slices parallel to the horizontal plane connecting the anterior and posterior commissures. For functional imaging, we acquired 34 slices in the same plane using a SENSE inverse spiral pulse sequence (TE = 32 ms, TR = 2000 ms, FOV = 25.6 cm^2, matrix = 64 × 64 × 34, 3.8 mm^3).

The following pre-processing steps were carried out using FEAT (FMRI Expert Analysis Tool) Version 5.92, part of the FSL analysis package (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl): slice-timing alignment, motion correction, coregistration, removal of nonbrain voxels using Brain Extraction Tool, normalization, smoothing (5 mm^3 kernel) and high-pass temporal filtering (1/60 Hz). Statistical results were thresholded at a voxel significance level of $z > 2.3$ and a whole brain-corrected cluster significance threshold of $P < 0.05$.

The general linear model used for the first-level FSL FEAT analysis contained three types of events: negative distractors, neutral distractors and targets. Results were combined across runs, for each subject, using fixed-effects models. For the main effect of negative emotion, we used the contrast *negative > neutral & target*, which was coded as (2, −1, −1). For the main effect of target, we used the contrast *target > (negative & neutral)*, which was coded as (2, −1, −1). We identified region of interests (ROIs) in our third-level analysis of treatment (ATD, control) by stimulus type (negative, neutral, target) using a fixed-effects model, and then subjected the ROIs to additional across-subjects analyses. For those analyses, we calculated the peak hemodynamic response (at 6 s post stimulus), compared with a baseline from −4 to 0 s. An ANOVA was conducted on each ROI using an alpha level of $P < 0.05$ (two-tailed; full Bonferroni correction across ROIs).

To investigate the association of behavioral memory performance with neural blood oxygen level-dependent (BOLD) signals, we used memory accuracy as a covariate in the GLM model using random-effects analysis (FLAME1). We defined memory accuracy as hit rate minus false alarm (FA) rates (Sharot *et al.*, 2007). (We note that similar regression analyses were conducted using mood and anxiety level as covariates, but those analyses revealed no significant results and are not discussed further).

RESULTS

Tryptophan and mood/anxiety measures

We successfully manipulated the plasma tryptophan level during the ATD session; the mean decrease in total plasma tryptophan level was 91% at the blood drawn immediately following the fMRI session (Figure 1).

The mood score measured by the VAS did not show significant differences between the 2 days, however, the Positive Affect (PA) score measured by the PANAS decreased on the ATD day at all measured time points compared with the control day. The decrease was significant from the control day both at 3 and 5 h following AA intake (Table 1). There was no significant change in the Negative Affect (NA) scores, the stress level or the arousal level. The anxiety level measured by STAT-state showed a significant decrease at the measurement immediately after completion of the fMRI scan, compared with the baseline measurement and those 1 and 2 h following scanning, suggesting a transient reduction in anxiety.

Behavioral performance

There was no ATD treatment or interaction effect on RT or response accuracy. Replicating the findings of Yamasaki *et al.* (2002), there was a significant effect of stimulus type on RT [$F(1,11) = 55.59$, $P < 0.001$] with significant RT differences among the four types of stimuli (Negative > Neutral > Target > Standard); all pairwise differences were significant at $P < 0.005$.

The valance and arousal ratings for the distracting pictures were not significantly different between the 2 days. We examined the consistency of each subject's valence ratings on the pictures with our original valence codes, which were derived from ratings by healthy subjects in the previous studies (Wang *et al.*, 2005). The valence ratings for each type

Table 1 Mood, stressfulness and arousal level across time

	Time	ATD	Control	Treatment effect	Time effect	Treatment × Time
PA	T0	22.4 (1.8)	26.3 (1.8)	$F = 3.92$, $P = 0.05$	$F = 1.90$, $P = 0.084$	$F = 0.76$, $P = 0.61$
	T1	21.2 (1.7)	24.1 (1.7)			
	T2	21 (1.9)	27.3 (1.9)			
	T3[a]	21.5 (1.7)	25 (1.7)	T3, ATD < Control		
	T5	20.5 (1.5)	24.6 (1.5)	T5, ATD < Control		
	T6	20.8 (1.7)	24.2 (1.7)			
	T7	23.3 (1.8)	25.3 (1.8)			
NA	T0	11.5 (0.9)	12.1 (0.9)	$F = 0.11$, $P = 0.75$	$F = 1.67$, $P = 0.13$	$F = 0.072$, $P = 0.99$
	T1	11.4 (0.6)	11.3 (0.6)			
	T2	11.1 (0.3)	10.7 (0.3)			
	T3	11.3 (0.4)	10.8 (0.4)			
	T5	11.9 (0.6)	11.6 (0.6)			
	T6	10.9 (0.5)	11.0 (0.5)			
	T7	11.6 (0.9)	11.8 (0.9)			
Stress (scores 1–7)	T0	2.2 (0.3)	2.3 (0.3)	$F = 0.24$, $P = 0.64$	$F = 2.95$, $P = 0.11$	$F = 0.54$, $P = 0.78$
	T1	2.2 (0.2)	1.6 (0.2)			
	T2	1.7 (0.3)	1.8 (0.3)			
	T3	2.1 (0.2)	1.9 (0.2)			
	T5	2.6 (0.3)	2.3 (0.4)			
	T6	1.8 (0.3)	1.9 (0.3)			
	T7	1.9 (0.3)	1.8 (0.3)			
STAI-state	T0	42.2 (1.3)	41.5 (1.2)	$F = 0.03$, $P = 0.96$	$F = 4.5$, $P < 0.001$	$F = 0.69$, $P = 0.66$
	T1	41.9 (1.1)	41.3 (1.1)			
	T2	40.4 (1.4)	41.5 (1.4)			
	T3	40.1 (1.3)	40 (1.2)			
	T5[a]	37.3 (1.4)	39.1 (1.3)		T5 < T0, T6 and T7	
	T6	41.2 (1.4)	40.8 (1.3)			
	T7	40.9 (1.8)	40.5 (1.7)			
Arousal (scores 1–9)	T0	3.2 (1.2)	3.2 (1.7)	$F = 0.16$, $P = 0.70$	$F = 1.32$, $P = 0.25$	$F = 0.069$, $P = 0.99$
	T1	3.3 (1.2)	3.4 (1.5)			
	T2	2.8 (0.9)	2.7 (1.0)			
	T3	3.2 (1.2)	3.2 (1.8)			
	T5	3.3 (1.2)	3.5 (1.7)			
	T6	2.9 (1.5)	3.3 (1.6)			
	T7	3.8 (1.9)	3.5 (1.6)			

[a]Bonferroni *post hoc* test revealed a significant difference between the two conditions or the time points. T0–T7 refers to time (hours) past since the amino acid intake.

of picture were highly consistent with the original valence codes, and did not differ between treatment days. In the control session, the match for negative pictures was 96% (s.d. = 1%), and the match for neutral pictures was 91% (s.d. = 2%). In the ATD session, the match for neutral pictures was 95% (s.d. = 2%), and the match for negative pictures was 92% (s.d. = 3%). Given this agreement, we used the *a priori* valence codes for further analyses.

The post-scan memory test revealed a negative memory bias in the ATD session. An ANOVA on the memory accuracy (hit rates minus FA rates) yielded a significant effect of emotion (negative minus neutral) and an interaction effect of emotion by treatment (Figure 2B). Participants correctly recognized more negative pictures than neutral pictures across the 2 days and had a stronger effect of emotion in the ATD session than in the control session (Table 2). When averaged across negative and neutral pictures, there was no main effect of treatment on memory accuracy; that is the averaged accuracy rate across negative and neutral pictures was similar for the ATD and control sessions. The correct rejection rate revealed a main treatment effect, indicating that the participants were better at discriminating new pictures (high correct rejection rate) and at discriminating new negative pictures on the ATD day than on the control day (Table 2).

To confirm that the increased correct rejection rate was due to increased sensitivity and not to a shift in decision criterion, we calculated the discrimination sensitivity (d') and the β choice bias ratio. We found a strong interaction effect on d' [$F_{(1,23)} = 12.13$, $P = 0.003$] such that there was better discriminability for negative pictures relative to neutral pictures on the ATD session than during the control session ($t = 2.87$, $P = 0.02$). We did not find a significant difference in the β ratio between the ATD session and the control session. Thus, we conclude that ATD led to better memory and improved discrimination for negative stimuli.

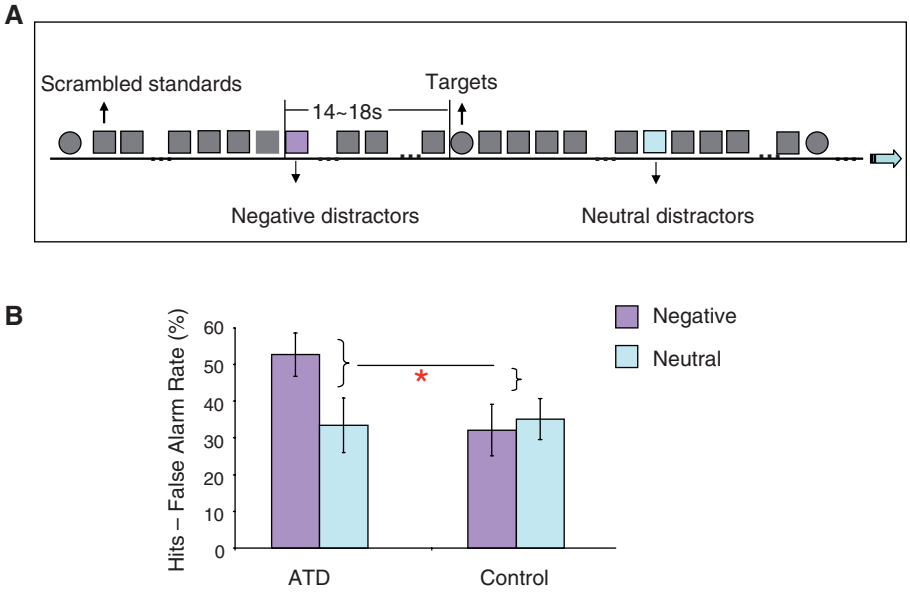

Fig. 2 (**A**) Illustration of the emotional oddball task (Wang et al., 2008); (**B**) Memory performance measured by memory accuracy (Hits—FA) on the subsequent memory test 1 h after the fMRI scan. During the ATD session, subjects exhibited an enhanced memory bias for negative pictures relative to neutral pictures. ∗ paired *t*-test, $P < 0.05$.

Table 2 The memory performance and ANOVA analysis

	ATD mean (s.d.)	Control mean (s.d.)	Treatment effect	Stimulus type effect	Interaction
Hits			$F(1,22) = 0.35$ $P = 0.56$	$F(1,22) = 14.5$ $P = 0.001$	$F(1,22) = 4.401$ $P = 0.048$
Negative	57.7 (20.4)	50.8 (19.6)			
Neutral	38.3 (24.2)	44.9 (21.6)			
Hits—FA			$F(1,22) = 0.35$ $P = 0.56$	$F(1,22) = 4.34$ $P = 0.047$	$F(1,22) = 10.01$ $P = 0.004$
Negative	52.8 (20.5)	32.2 (24.2)			
Neutral	33.4 (25.6)	35.1 (19.2)			
Correct rejection			$F(1,22) = 4.43$ $P = 0.047$	$F(1,22) = 4.99$ $P = 0.036$	$F(1,22) = 3.99$ $P = 0.036$
Negative	95.1 (4.3)	81.3 (18.3)			
Neutral	95.2 (4.6)	90.2 (13.7)			

Notes: All planned paired comparisons were significant ($P < 0.05$).

fMRI results

The ANOVA analyses (Table 3) revealed significant main effects of *treatment (ATD, control)* and *stimulus type (negative, neutral, target)*. Collapsing across stimulus types, ATD significantly increased activation in the inferior frontal gyrus (IFG, BA45), dorsomedial prefrontal cortex (dmPFC) and dorsal anterior cingulate cortex (dACC, BA32) (Figure 3).

The ANOVA analyses yielded a significant main effect of *stimulus type* (Table 3). The negative stimuli induced significantly stronger activation in the dmPFC, vmPFC (ventromedial prefrontal cortex), bilateral ventrolateral prefrontal cortex (vlPFC, both BA45 and BA47), bilateral middle temporal cortex, hippocampus, bilateral fusiform gyrus and precuneus. The target stimuli revealed significantly greater activation in the dlPFC, dACC, insula, motor and sensory cortex, supplementary motor cortex (SMA), inferior parietal cortex and cerebellum. In summary, the effect of *stimulus type* confirmed our previous findings that the task activated the ventral emotional system in response to negative stimuli and activated the dorsal executive system in response to attentional targets (Yamasaki *et al.*, 2002; Wang *et al.*, 2005).

The interactive effect of *treatment by stimulus type* was found in the left orbital part of the IFG (orbital-IFG, BA47), dmPFC and bilateral angular gyrus and middle temporal cortex areas (Table 3, Figure 4). All of these regions revealed stronger activation to negative distractors than to neutral distractors or targets across both sessions ($P < 0.001$ in all comparisons). All three regions also showed significantly stronger activations for negative stimuli in the ATD session compared with the control session. That is, ATD selectively increased activation to negative distractors in these regions.

Targets evoked de-activation in the dmPFC and the angular gyrus (AG) in the control condition, and ATD evoked deeper deactivation to targets in the dmPFC (Figure 4B). The differential de-activation in these regions was confirmed using a voxel-based paired *t*-test on the activation in response to targets. Notably, the ATD-induced enhancement

Table 3 Regions showing a main effect or an interaction effect using voxel-based analysis (cluster corrected, $Z > 2.3$, $P < 0.05$)

	Cluster size	Regions and Subregions	BA	*X*	*Y*	*Z*	*z* -value
Treatment effect							
ATD > Control	657	Right SMA	BA6	2	10	64	4.03
		Right ACC	BA24	12	26	28	4.03
		Right middle cingulate cortex	BA32	8	16	36	3.71
		Left SMA	BA32	−2	6	52	3.71
	415	Left IFG	BA13	−38	10	14	4.1
		Left IFG	BA46	−44	18	26	4.05
			BA45	−54	12	22	3.48
		Left insula	BA13	−38	18	8	3.6
Stimulus effect							
Negative > Neutral & Target	21 745	Right inferior occipital cortex	BA18	42	−82	−2	22.3
		Right cuneus	BA17	14	−96	10	20.8
		Right calcarine	BA17	16	−92	2	20.2
		Right middle occipital cortex	BA19	34	−84	10	19.7
		Right fusiform gyrus	BA19	30	−58	−10	15.1
		Left calcarine	BA17	−12	−94	−2	20.6
		Left fusiform gyrus	BA19	−30	−54	−14	16.8
	2580	Left dmPFC	BA10	−8	62	28	8.79
			BA9	−6	58	32	8.3
			BA8	−6	50	44	8.27
	2520	Left IFG	BA45	−50	26	14	8.91
		Left orbital-inferior frontal	BA11	−26	30	−20	7.6
	1322	Right IFG	BA45	56	28	4	8.68
		Right orbital-inferior frontal	BA47	26	28	−14	7.25
		Left vmPFC	BA11	−4	44	−18	8.41
	703	Right vmPFC	BA11	4	44	−20	8.07
		Left hippocampus		−22	−10	−16	3.92
		Right posterior cingulate	BA31	2	−56	24	7.63
Target > Negative & Neutral	47 697	Left postcentral cortex	BA40	−42	−36	58	14.2
		Left precentral cortex	BA6	−32	−22	68	11
		Right inferior parietal cortex	BA40	44	−48	54	10.8
		Right dlPFC	BA10	34	46	22	8.12
		Left dlPFC	BA10	−38	48	26	7.56
		Left SMA	BA6	−2	−8	54	8.90
		Right insula	BA13	36	−4	14	6.85
		Left ACC	BA32	−8	32	22	6.12
		Left precuneus	BA7	−6	−68	52	6.64
		Cerebellum		−6	−66	−8	5.66
Treatment × Stimuli							
Negative > Neutral & Target ATD > control	874	Left dmPFC	BA9	−6	58	34	4.17
		Right dmPFC	BA9	4	44	34	3.69
	703	Left middle temporal cortex	BA39	−46	−66	22	4.04
		Left angular gyrus	BA39	−48	−70	26	3.95
		Left supramarginal gyrus	BA40	−52	−48	24	3.34
	570	Right middle temporal cortex	BA22	50	−60	12	4.25
		Right angular gyrus	BA39	48	−60	26	4.25
	552	Left orbital-inferior frontal	BA47	−46	24	−10	4.47
		Left orbital-orbital frontal	BA47	−44	34	−2	3.36

ACC, anterior cingulate cortex; IFG, inferior frontal cortex. *x, y, z* were in the Montreal Neurological Institute (MNI) space.

of de-activation in response to targets occurred in the default-mode network regions including: dmPFC, posterior cingulate and orbital-IFG (BA47).

Correlations of neural activation with subsequent memory performance

In the ATD session, the memory accuracy score (hit rate minus FA rate) for both negative and neutral distractors was significantly correlated with activations in the visual cortex, fusiform gyrus and frontal regions including bilateral IFG, dACC and dmPFC (Table 4). However, during the control session, better memory performance was only correlated with activation in visual regions, and not with the frontal regions (Figure 5). ROI- based ANCOVA analysis using treatment (ATD, control) and memory performance as covariates (SPSS 15.0) confirmed a significant difference in the correlation of frontal activation with the memory performance between ATD and controls (left IFG,

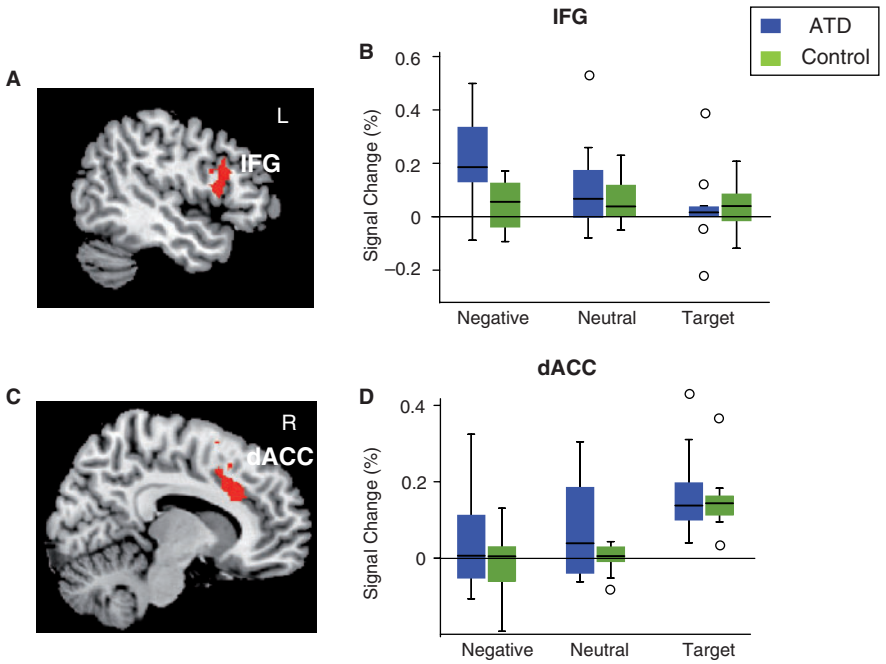

Fig. 3 Regions which showed significant treatment effect (cluster corrected, $P < 0.05$), i.e. ATD> control session regardless of stimulus types (**A** and **C**) and nonindependent ROI box-and-whisker plots in these regions (**B** and **D**). (A and B) IFG, the inferior frontal gyrus (BA45); (C and D) dACC, dorsal anterior cingulate. There were significant treatment and stimulus type effects in both regions. The IFG was selectively activated by the negative distractors and the dACC was mainly activated by the targets.

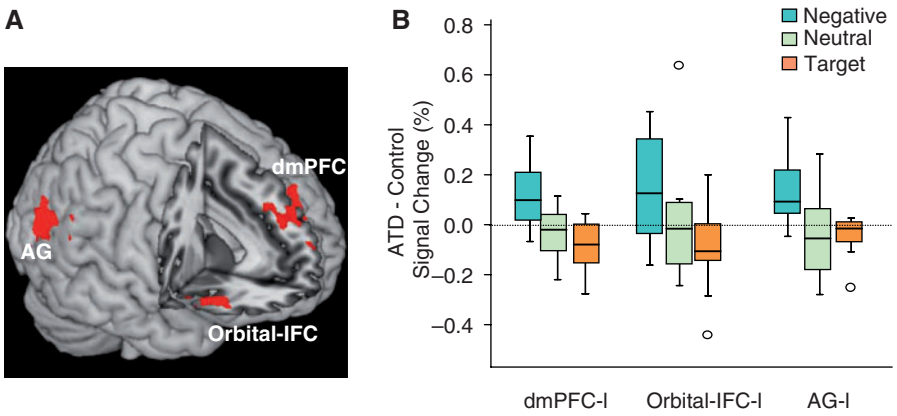

Fig. 4 Regions which showed significant interaction effect (cluster corrected, $P < 0.05$) of treatment (ATD, control) × Stimulus type (Negative, Neutral, Target) using the voxel-based ANOVA analysis (**A**) and nonindependent ROI box-and-whisker plots in these regions (**B**) illustrating the BOLD signal change difference between ATD–control in response to each stimulus type. AG, Angular gyrus.

$F = 5.775$, $P = 0.026$; dmPFC, $F = 4.538$, $P = 0.045$, Figure 5). Using independent ROIs based on the main effect of treatment (ATD, control) from the ANOVA analysis also confirmed the correlation (Figure 6, ATD, $r = 0.76$, $P = 0.004$; Control, $r = 0.05$, $P = 0.88$). We further tested whether or not the decreased PA could confound our results. We thus included the PA scores as a covariate in our analyses, and the effects of treatment day (i.e. as shown in the plots of Figures 5 and 6) were still significant. Thus, despite similar memory performance when collapsing negative and neutral stimuli, ATD led to increased frontal activation compared to the control session. The correlations were not specific to negative distractors, but were robust across both distractor types.

DISCUSSION

The present study examined the effect of low brain tryptophan levels on emotional memory and executive function through acute tryptophan depletion. Consistent with our hypotheses, we found that ATD enhanced memory for negative pictures relative to neutral pictures (i.e. led to a negative memory bias) and increased activation to negative relative to

Table 4 Regions showing significant correlation with the strength of activations to distractors in voxel-based analysis (cluster corrected, $Z > 2.3$, $P < 0.05$)

Regions and subregions	BA	Cluster size	*X*	*Y*	*Z*	*z*–value
Right fusiform gyrus	BA37	10 835	36	−60	−6	9.61
Right superior occipital cortex	BA39		32	−72	26	8.7
Left fusiform gyrus	BA37		−40	−60	−16	9.13
Left cuneus	BA19		−28	−88	24	9.43
Left IFG	BA46	4633	−40	20	22	8.92
Left orbital-IFG	BA13		−44	22	−8	8.04
Right IFG	BA46	2563	48	18	24	9.78
Right SMA	BA6	1793	2	12	46	7.22
Right dACC	BA32		6	20	34	6.89
Left dmPFC	BA10	387	−8	62	14	5.61

dACC = dorsol anterior cingulate cortex. *x*, *y*, *z* were in the MNI space.

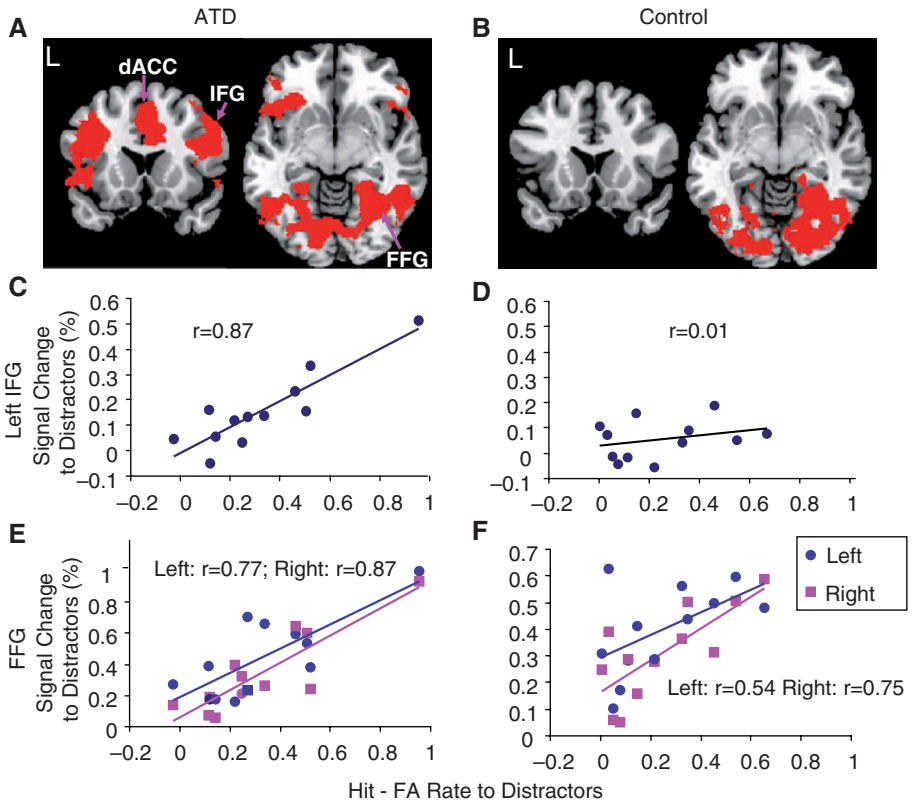

Fig. 5 Brain activation maps: regions where activations were significantly correlated with memory for distractors in the ATD (**A**) and control (**B**) sessions (cluster corrected, $P < 0.05$); Plots showing the relationship of the memory accuracy (Hit-FA rate in *x*-axis) with the strength of activation (signal percentage change in y axis) in response to distractors in the left IFG (**C** and **D**) and the left and right FFG (blue and magenta dots, respectively) (**E** and **F**). (C and E) are results from the ATD session and D and F are results from the control session. The control session only revealed correlations in the visual areas, whereas the ATD session showed strong correlations in the frontal regions as well. The non-independent ROIS were derived from the voxel-based whole-brain analysis. FFG, fusiform gyrus.

neutral pictures in the left orbital-inferior frontal area (BA47), dmPFC and bilateral angular gyri. ATD also enhanced de-activation in the default-mode network regions during target detection, but did not influence target-detection performance. Additionally, ATD induced nonstimulus specific effects in the form of stronger activations in the left IFG (BA45) and anterior cingulate (BA 32), regardless of stimulus type, that were correlated with overall memory performance.

Our results reveal enhanced memory for negative images relative to neutral images following ATD. Although we did not find a linear correlation of brain activation with the negative memory bias in the ATD session, we did find selectively greater activation to negative relative to neutral

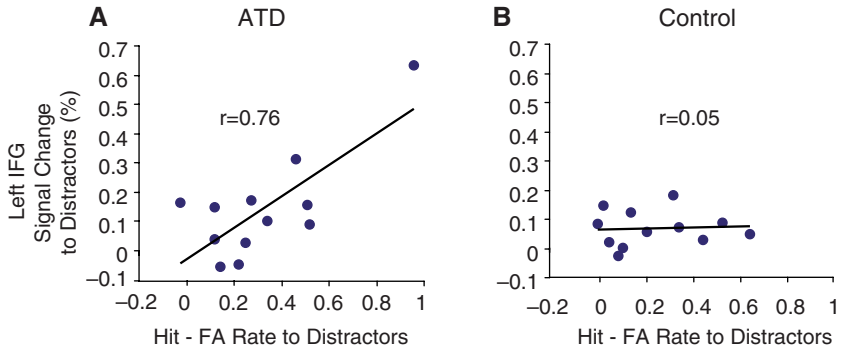

Fig. 6 Plots (**A** from the ATD session, **B** from the Control session). Plots confirming the relationship of the memory accuracy (Hit-FA rate in *x*-axis) with the strength of activation (signal percentage change in *y*-axis) in response to distractors in the left IFG using independent ROI defined by significant clusters which showed the main effect of treatment (ATD, control) from the ANOVA analysis (cluster corrected, $P < 0.05$). IFG = inferior frontal gyrus

distractors in the left orbital-IFG (BA47), dmPFC and bilateral middle temporal cortex areas during the ATD session. The pattern of neural activities in these regions (bar graph of Figure 3) was consistent with the pattern of memory performance (Figure 2). Therefore, selectively increased activation to negative distractors in these regions during encoding might account for the negative memory bias in the ATD session.

The alteration of activations in the left orbital-inferior frontal gyrus (BA47), dmPFC and middle temporal cortex has been frequently reported in depressed patients (Steele *et al.*, 2006; Fitzgerald *et al.*, 2007), although the direction of changes varies depending on the task and the subjects' clinical status. Using a lenient threshold, we previously found that depressed patients showed increased activation in the orbital-IFG (BA47) when responding to negative stimuli during the emotional oddball task (Wang *et al.*, 2008). The ATD-induced hyper-activation in the orbital-IFG in the current study suggests that low serotonin levels could be responsible for the increased activation observed in depressed patients in response to negative stimuli. Activity changes in these regions in healthy volunteers have also been reported in ATD studies using other types of tasks (Roiser *et al.*, 2006; Fitzgerald *et al.*, 2007).

Although ATD increased activation within the left IFG (BA45) and dACC in a task content-independent fashion, the bar graph in Figure 3 reveals that the effect was mainly driven by increased activation to the distractors during ATD. Furthermore, those who showed stronger activation in these frontal regions also had better memory for the distractors, regardless of distractor valence (Figure 5). The left IFG has been associated with successful inhibition of distraction (Dolcos *et al.*, 2006), and the dACC has been associated with attention, error detection and online-monitoring (Carter *et al.*, 1998). Given that the RT and accuracy for target detection were comparable between the ATD and control sessions, we speculate that the enhanced frontal activations in our study were related to effortful recruitment of neural activity in these regions for successful encoding of the distractors due to stronger NA induced by the images while maintaining the constant task performance for target detection. Consistent with this interpretation, Evers and colleagues also found that ATD increased activation in the dmPFC during negative feedback (Evers *et al.*, 2005). As an alternative possibility, the enhanced activation in the IFG to negative stimuli could also be due to stronger NA induced by the images *per se* under ATD.

Collectively, we found that ATD led to more target-induced de-activation in regions of the default network (Raichle *et al.*, 2001; Greicius *et al.*, 2003). The task-induced default activity has been linked to the interruption of ongoing internal processing and a re-allocation of processing resources (Raichle *et al.*, 2001; Greicius *et al.*, 2003). McKiernan and colleagues reported that the magnitude of task-induced de-activation increased with task demands during an auditory target detection task (McKiernan *et al.*, 2003). Thus, enhanced default negativity in the dmPFC and posterior cingulate during target detection in the ATD session could be a consequence of increased task demands in attentional re-allocation under tryptophan depletion (Ahveninen *et al.*, 2002). Unlike depressed patients who showed decreased activation to targets in the dlPFC and slowed RT while performing this task (Wang *et al.*, 2008), the changes in healthy subjects under ATD are too subtle to affect positive activation in the executive system or to affect behavioral performance.

A major limitation of our study was our use of an open-label design. Theoretically, open knowledge of the experimental design could confound many of the measurements in the study (e.g. the reduced happiness at onset of the ATD day). However, we suggest that this design limitation cannot account for all of our results for three reasons. First, the low PA score was fairly constant during the ATD day rather than varying with tryptophan levels. Thus, we included positive affect scores as a covariate in our analyses, and the core conclusions of the study were still obtained. Second, there were no significant differences in stress, arousal or anxiety scores between the two days. Third, ATD specifically

enhanced memory to negative pictures but not neutral pictures, reflecting an interaction of ATD by emotional valence, not a main effect of ATD. As is true for all ATD studies, there is a possibility that the findings during the ATD condition are not purely a result of low serotonin, but rather reflect interactive effects of acute low serotonin on other neurotransmitters (Praschak-Rieder *et al.*, 2005). Nevertheless, the findings using the open-label design provided a new addition to the literature, confirming effects of ATD on emotion and cognition.

In summary, we found that ATD did not cause a generalized decrement in memory performance. Rather, ATD selectively enhanced memory for negative stimuli, with concomitant increases in activation in frontal cortex. Together with enhanced de-activation in the default network, these results support the conception that ATD both alters brain systems for affective processing and leads to compensatory changes in brain systems for cognitive control.

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