

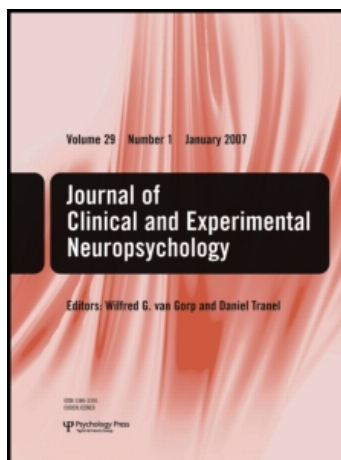
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A synergic effect between lowered serotonin and novel situations on impulsivity measured by CPT

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Rapid tryptophan depletion studies investigate serotonin using amino acid precursor depletion, which transiently reduces the brain level of serotonin. This study compares the effects of serotonin reduction given on the first test day (when the situation is novel) with the effects of serotonin reduction given on the second test day (when the environment and test battery are familiar). A total of 24 healthy young males were given either active tryptophan depletion or placebo in this randomized cross-over design, while impulsivity was measured by a continuous performance test. The participants showed more impulsive responses and reduced attention during tryptophan depletion, but only when this was given on the first test day when the task was novel. This could be caused by a synergic effect between novel situations and reduced neurotransmission of serotonin.

INTRODUCTION

Novel and familiar situations occasionally elicit different behavior. On a biological level, this effect might be related to the neurotransmitter serotonin. Reduced serotonin levels have previously been associated with impulsivity. Thus, reduced serotonergic activity relates to impulsivity in male offenders (Doland, Anderson, & Deakin, 2001), impulsive arsonists (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987), impulsive behavior in personality disordered subjects (Coccaro & Kavoussi, 1997), and depressed patients with a history of violent, impulsive suicide attempts (Asberg, 1997). Since these studies are retrospective association studies, it is important to devise intervention studies that may obtain more direct evidence of a causal effect. Rapid tryptophan depletion (RTD) studies, coupled with a laboratory method to measure impulsivity, allow for such research. Tryptophan is the precursor of serotonin, and a large body of data shows that depletion of tryptophan reduces brain serotonin content and function (Hood, Bell, & Nutt, 2005).

Novel test materials provide increased sensitivity to detect frontal-lobe damage on neuropsychological tests, such as Trail Making Test, Part A (Demakis, 2004). An increased effect when using a new test in a novel environment has also been found in animal studies manipulating serotonin. Several studies have shown that intact or increased serotonergic activity is required for animals to explore novel environments and function optimally, while fewer changes in animal behavior in response to altered serotonergic activity are observed when the animal is in a familiar, secure environment (Bourin & Hascoet, 2003; Geyer, 1996). Studies on rats have shown increased reactive behavior on the forced swimming test following the administration of parachloroamphetamine (PCA), which reduced the level of serotonin (Harro, Tønissaa, Eller, Kask, & Orelund, 2001). However, this effect of increased reactivity was only observed when the rats were exposed to PCA during the first swimming session. Harro (2002, p. 433) notes: "This temporal reduction of immobility cannot be interpreted as a reduction of behavioral

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despair, an active coping strategy, or a learning effect, and as a working hypothesis, we suggest that it reflects an increase in 'reactive' or 'impulsive' behavior." Furthermore, PCA-treated rats would also show enhanced muricide (mouse killing), provided the exposure to mice was a novel experience (Soubrié, 1986). Since previous exposure of mice to rats cancelled the increase in muricidal behavior, it was suggested that decreased serotonergic transmission does not increase aggression per se, but rather facilitates the expression of aggressive impulses in novel situations.

Thus, one might expect that a decrease in serotonin levels would exert a more pronounced effect on impulsivity in novel than in familiar environments. In other words, behavioral measures might be more sensitive to alterations in serotonin metabolism when they occur in novel environments. We are not aware of any human studies that have examined differential effects of altered serotonergic levels in novel versus familiar conditions with respect to impulsivity.

There is a general consensus in the field that impulsivity is multifactorial, but there is little agreement as to what these factors are (Evenden, 1999). Dougherty et al. (2003a) and Swann, Bjork, Moeller, and Dougherty (2002) investigated personal and clinical characteristics of impulsivity and found that the neuropsychological tests that best predicted these measures were of the rapid-response impulsivity type. The continuous performance test (CPT) is a typical test measuring rapid-response impulsivity, and it requires the individual to make rapid evaluation/discrimination of presented stimuli to decide whether or not to respond (Dougherty, Mathias, & Marsh, 2003b). Traditionally, the indices most widely used to assess performance on the CPT have been correct responses to target stimuli ("hits") and responses to nontarget stimuli ("false alarms"). False alarms are strongly linked to impulsivity (Dougherty et al., 2003a; Dougherty et al., 2003b; Dougherty et al., 2004; Swann et al., 2002).

In this study we used a within-subjects, cross-over study design in which each participant was given active tryptophan depletion and placebo, each on one of two separate test days. Thus, it could be tested whether individuals exposed to RTD during the first test day (when the situation is novel) might be more sensitive to the serotonin-lowering effect of RTD than are individuals exposed during the second test day (when the situation is familiar). Exposing individuals to RTD, we expected impulsivity, as measured on a continuous performance test—identical pairs (CPT-IP), to be more pronounced in a novel, rather than a familiar, environment.

METHOD

Participants

A total of 24 males (aged 21 to 29 years; mean 25 years) were recruited from medical and psychological students at the University of Oslo. They had an average of 4 years of university education, and all signed a statement that they were drug free, healthy, and without any history of psychiatric problems. All the participants completed the experiment. The study was carried out in accordance with the Helsinki Declaration, the regional ethics committee reviewed it, and all the participants signed an informed consent.

Amino acid mixtures

The procedure for RTD has been described in detail elsewhere (Hood et al., 2005; Walderhaug et al., 2002). In brief, the participants ingested a 100-g mixture of amino acids devoid of tryptophan. This stimulated protein synthesis by the liver, and the preexisting available tryptophan was incorporated into the newly synthesized proteins. This led to an 80–90% reduction of serum tryptophan within 5–6 hr. The three most foul-tasting amino acids were ingested in capsules. In placebo or sham depletion, tryptophan-containing capsules were ingested, while these capsules contained lactose during active depletion. Both the participants and the researchers were blind to the content of these tasteless, similar-looking capsules.

Experimental schedule

The participants received written information and were reminded again the day before the experiment not to drink alcohol, to eat low-protein food approximately 18hr before the start of the experiment, and to fast from midnight. The sessions started at approximately 9 a.m. with blood sampling and ingestion of the amino acids. During the ensuing 5-hr period, the participants were encouraged to read or watch emotionally neutral videos. The experimental paradigm was administered following the second blood sample, approximately 6.5hr after the ingestion of the mixture, when the plasma concentration of tryptophan was expected to be at the lowest. The participants were randomized to receive either the active or placebo capsules first and then, after an average of 9 days (minimum 5 days), crossed over to otherwise identical experimental conditions.

Experimental paradigm

The CPT-IP is a transient-attention, sustained-response preparation task (Smid, de Witte, Homminga, & van den Bosch, 2006). The CPT-IP was employed to measure false alarms, our indicator for impulsivity (Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989). The CPT-IP generated visual stimuli on a computer monitor and recorded responses. The participant's task was to quickly respond whenever two identical stimuli were presented in a row. The CPT-IP was divided into two modes: The first produced successively 150 four-digit numbers (the number mode), and the second presented a string of 150 nonsense shapes (the shapes mode). Each stimulus was presented at a constant rate of one per second, with a duration of 50 ms. A total of 30 of the trials (20%) in each mode were target trials and required a response.

A correct identification of a matching set is termed "hit." Each condition also included a number of catch trials in which the stimulus presented was very similar, but not identical, to the preceding stimulus. Responses to catch trials were considered a specific type of commission error, referred to as "false alarms" (Cornblatt et al., 1989). Signal detection analysis combines hits and false alarms into d' (d prime) and β (beta). These two signal detection parameters are increasingly used for human information-processing tasks, providing a valuable tool for summarizing the data in a format that represents participants' sensitivity to stimuli (d') and participants' response style (β). This allows controlling for false positive or negative data in cases where the participants are unengaged in the task and provide responses in a purely randomized manner. The β value is a measure of response style, an indicator of the competition between behavioral suppression and active responding. The d' value is a measure of the subject's ability to discriminate between stimuli and involves the observer's attention and sensory capacity (Davies & Parasuraman, 1982; Swets, Tanner, & Birdsall, 1961). Dependent measures for the number and shape mode are hits given as percentage of the 30 target trials, and false alarms given as percentage of the catch trials. The two signal detection parameters d' and β are also reported.

Data analysis

To test whether individuals exposed to RTD during the first test day (when the situation is novel) are more sensitive to the serotonin-lowering effect of RTD than are individuals exposed during the

second test day (when the situation is familiar), the participants were divided according to the order in which they were given the active interventions. A paired-sample t test was used to examine the differences between active tryptophan depletion and placebo in each group. The data were further analyzed for ordering effects using repeated-measures analysis of variance (ANOVA) with group (active depletion first and sham depletion second, or sham depletion first and active depletion second) as the between-subjects factor and treatment (active or sham depletion) as the within-subjects factor. Any interaction indicates that the participants start the second day of the experiment in a dissimilar state, and this will make it necessary to discard the data collected the second test day and to conduct an independent samples t test on the first-session data only (Hills & Armitage, 1979).

RESULTS

Rapid tryptophan depletion

The active depletion significantly decreased plasma concentrations of free and total tryptophan relative to baseline by 85% and 83%, respectively. The successful intervention was similar to that previously reported in healthy control subjects (Ellenbogen, Young, Dean, Palmour, & Benkelfat, 1996; Hood et al., 2005; Riedel, Klaassen, & Schmitt, 2002). The ratio of free and total tryptophan versus the other large neutral amino acids (LNAA) fell 92% and 91% during active depletion. The mean serum concentrations of each of the amino acids before the ingestion of the amino acid drink and 5 hr after ingestion have been published previously (Walderhaug et al., 2002).

RTD on the first or the second test day

The 12 participants who had experienced the active depletion first and sham depletion second were compared with those 12 who experienced the sham depletion first and active depletion second. There were no differences in age, years of education, degree of tryptophan depletion, or washout period. Results are shown in Table 1. The participants given the active intervention on the first test day, with placebo on the second, were more impulsive when tryptophan was depleted than they were when given the placebo intervention. This was reflected in a higher rate of false alarms in the number mode, $t(11) = 3.2$, $p < .01$, and the shape mode, $t(11) = 2.7$, $p < .05$. In addition, a higher response rate to both correct and incorrect stimuli

TABLE 1
The means and standard deviations for the dependent variables

Variable	Active/placebo	Day 1		Day 2		
		Mean	±SD	Mean	±SD	
Numbers	False alarms ^a	Active	36	±12	19	±14
		Placebo	22	±14	26	±16
	Hits ^a	Active	83	±15	88	±9
		Placebo	84	±13	75	±17
	<i>d'</i>	Active	1.40	±0.71	2.26	±0.82
		Placebo	1.98	±0.78	1.51	±1.06
Beta	Active	0.62	±0.22	0.80	±0.48	
	Placebo	0.93	±0.82	1.02	±0.37	
Shapes	False alarms ^a	Active	33	±22	15	±13
		Placebo	26	±20	17	±16
	Hits ^a	Active	81	±11	85	±14
		Placebo	89	±11	91	±8
	<i>d'</i>	Active	1.44	±0.67	2.32	±0.92
		Placebo	2.13	±0.88	2.50	±0.67
Beta	Active	0.93	±0.41	1.24	±1.19	
	Placebo	0.68	±0.43	0.93	±0.62	

Note. SD = standard deviations.

^aIn percentages.

in the number mode occurred, resulting in a decreased beta signal detection variable, $t(11) = 4.7, p < .001$, when the participants were depleted. Furthermore, the group given the active intervention first had reduced d' , $t(11) = 7.0, p < .001$, and reduced number of hits, $t(11) = 3.0, p < .05$, in the shape mode when depleted. There were no significant differences between the active and placebo condition on these or other variables in the group of participants given placebo on the first test day and active tryptophan depletion on the second.¹ This indicates that the group given placebo on the first test day did not have any statistically significant learning effects on the CPT-IP.

CPT: Order effects on false alarms and spatial d'

Significant interactions between the order of treatment and intervention emerged on the false-alarms measure, both for the number mode, $F(1, 22) = 9.6, p < .01$, and the shape mode, $F(1, 22) = 11.7, p < .01$. There was also a significant interaction for d' in the shape mode, $F(1, 22) = 20.4, p < .01$, demon-

strating an ordering effect for these variables. As shown in Figure 1, these interactions were predominantly due to more extreme scores when the task was novel—that is, were evidenced only in participants who experienced active depletion on the first test day.

CPT: First-session data

Due to the order effect on the spatial mode d' and both false-alarm variables, it was necessary to discard the data collected the second test day and re-analyze these three variables using an independent-samples t test on the first-session data only (Hills & Armitage, 1979). The participants given active intervention committed more false alarms, $t(23) = 2.7, p < .05$, than did the participants given placebo on the number mode, but not in the shape mode. The depleted participants showed a smaller d' , $t(23) = 2.2, p < .05$, in the shape mode, indicating that active intervention reduced their ability to discriminate between visuo-spatial stimuli.

DISCUSSION

The results indicate that reduced serotonin levels result in increased levels of impulsivity and impaired attention in a group of participants given active tryptophan depletion on the first test day, placebo on the second. The group receiving placebo on the first test day did not show such a response when active tryptophan depletion was

¹There were no significant differences between the active and placebo conditions in the group of participants given placebo on the first test day and active tryptophan depletion on the second for numbers: false alarms, $t(11) = 1.1$; hits, $t(11) = 1.1$; d' , $t(11) = 1.3$; beta, $t(11) = 0.7$; or shapes: false alarms, $t(11) = 2.1$; hits, $t(11) = 1.4$; d' , $t(11) = 0.8$; beta, $t(11) = 2.1$.

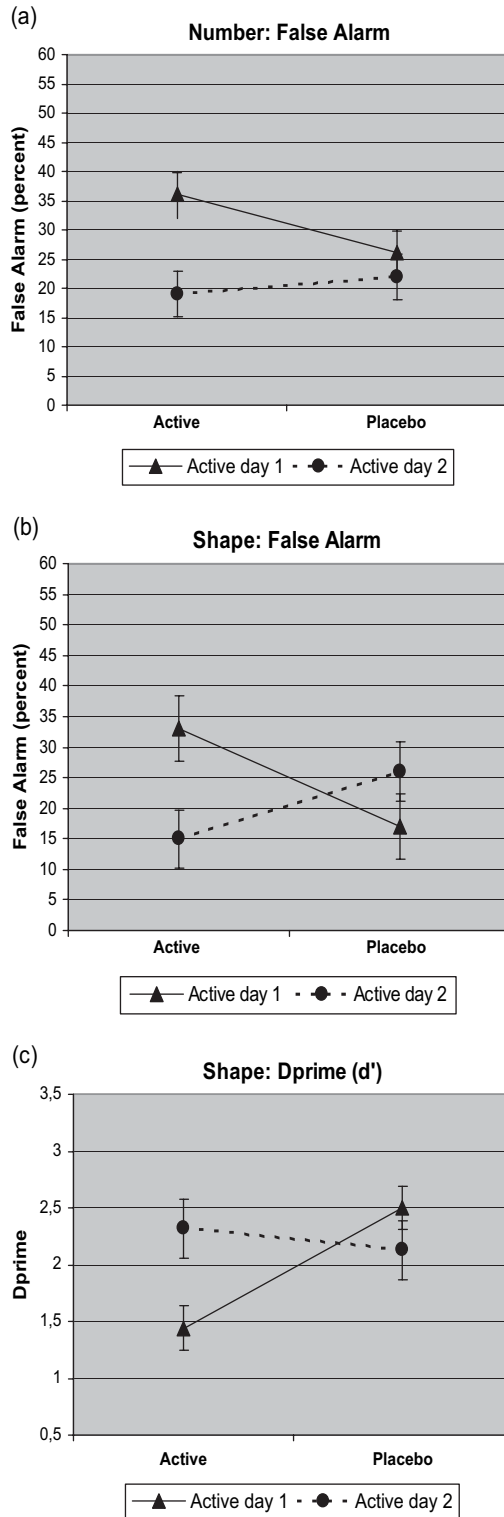


Figure 1. Means and SEM for (a) false alarms, numbers, (b) false alarms, shapes, and (c) d' shapes of the continuous performance test. The false alarms are given as percentage of catch trials. The changes are by day of exposure to active tryptophan depletion, in measures of impulsivity (false alarm) and accuracy (d'). The “Active Day 1” group was given the active tryptophan depletion on the first test day; the “Active Day 2” group was given placebo on the first test day.

administered on the second test day. The increased sensitivity to serotonergic depletion under novel circumstances was further demonstrated by significant interactions for both false-alarm variables and the spatial-attention variable (d'). These interactions were caused by increased false alarms and decreased d' when the participants were depleted, but only when the task was novel (see Figure 1).

The unique effect of tryptophan depletion on the first test day was not caused by compounds still present in the body. RTD is a dietary intervention, and its effects last only until the ingestion of a tryptophan capsule, which was always given at the end of our experiment. Even if the tryptophan capsules were not ingested, the serum tryptophan level would normalize following the first meal. This RTD study had a minimum of a 5-day washout period, making a biological carry-over effect quite improbable.

A learning effect in this study would be apparent if the test results were enhanced for both groups on the second test day. No statistically significant learning effect was observed in the group that received placebo first and active intervention second. However, due to low statistical power, one should be somewhat cautious in interpreting this null finding as evidence against a practice effect. It is possible that the interaction was partly influenced by the nonsignificant decrease in false alarms in the group that received placebo first and active intervention second. Nevertheless, the statistically significant difference in false alarms shapes, false alarms numbers, and d' occurred only in the group receiving active serotonin reduction on the first test day (see Figure 1). It is thus likely that the combination of active RTD and the novel situation resulted in an unusually high frequency of false alarms (and consequently low d'), which regressed to more normative scores on the subsequent test day.

Our data clearly indicate a synergic effect between lowered serotonin and novel situations on impulsivity. A hypothesis by Jacobs and Fornal (1999) postulates that serotonin serves as a “switch” between facilitating motor output and sensory information processing. Serotonin is tentatively suggested to have an integrative overarching function where it either facilitates motor output and suppresses sensory information processing or, reversely, disfacilitates motor output and disinhibits sensory information processing. This is in agreement with Soubrié’s observation that: “all the situations that are highly responsive to serotonin manipulation involve a degree of competition between behavioural suppression and active responding” (Soubrié, 1986, p. 328). Examining

electrophysiological activity of brain serotonergic neurons in cats, Jacobs and Fornal (1993) found that serotonergic cells fired rapidly during repetitive gross body movements such as walking, and, conversely, cell firing was suppressed when the animal orients to a strong sensory stimulus. In fact, during orientation to novel stimuli, the activity of the serotonergic neurons in the dorsal raphe nucleus and nucleus centralis superior would fall silent for several seconds. It is possible that the combination of active RTD and novel events reduces the neuronal release of serotonin below some threshold.

Poor impulsivity control is an integral part of attention deficit hyperactivity disorder (ADHD). The dopamine system has been implicated in ADHD (Solanto, 2002) and in novelty-seeking behaviour (Ebstein, Zohar, Benjamin, & Belmaker, 2002). Since the serotonin and dopamine systems interact at several levels in the central nervous system (Ebstein et al., 1998; Kapur & Remington, 1996; Wang, Ashby, & Zhang, 1996), the interaction of impulsivity and novelty found in this study might partly be mediated through the effect of serotonin on the dopamine system.

It has been suggested that RTD must reduce free plasma tryptophan by 60% or more in order to have an effect (Van der Does, 2001), and later studies seem to confirm this (Booij et al., 2005). We propose that the unique effect of RTD on the first test day could be caused by the new situation, or the novel series of stimuli, transiently reducing the neurotransmission of serotonin. This novelty induced reduction in combination with the active RTD, reduces the availability of serotonin past a critical threshold, causing the synergic effect between lowered serotonin and novel situations seen in our study, and in other studies as well.

In retrospect, a pattern similar to the findings of this study may be found in reexamination of four earlier RTD cross-over studies: On the first test day, tryptophan-depleted participants committed more errors and trials to reach criterion on an attentional set shift test (Park et al., 1994), showed increased response time on reversal learning in a visual discrimination task (Murphy, Smith, Cowen, Robbins, & Sahakian, 2002), and showed reduced level of cooperation in a prisoner's dilemma game (Wood, Rilling, Sanfey, Bhagwagar, & Rogers, 2006), and females responded with a lowering of mood (Ellenbogen et al., 1996; Smith, Clifford, Hockney, Clark, & Cowen, 1997), but only when the tryptophan depletion procedure, the tests, and the environment were novel. Hughes et al. (2003) notes that the RTD effect could be order dependent, and that any negative effects

(such as those described above) are magnified if active RTD is given on the first test day, while any positive effects are magnified if active RDT is given on the second test day. Taking these observations into consideration, there might be a more general link between reduced serotonergic transmission and novelty.

One of the implications of this study is that data from earlier tryptophan depletion studies with cross-over designs might be re-analyzed using repeated measures ANOVA with group (active depletion first and sham depletion second, vs. sham depletion first and active depletion second) as the between-subject factor. Hills and Armitage (1979) state: "to choose a cross-over is to take a chance. If the results of the trial suggest a definite interaction between treatment and periods then . . . the treatment comparison should be based on the first period alone" (p. 19). This procedure is essential for all cross-over designs and could uncover some Type II errors. Using this procedure on our interactions, we found that the tryptophan-depleted group responded with more false alarms in the verbal mode and displayed reduced attention in the spatial mode when comparing the results of the first test day only. Failing to cater for the effects of novelty, it is possible that the absence of statistically significant findings using cross-over designs have been misinterpreted in other studies. A study by Clark et al. (2005) concludes that serotonergic neurotransmission is not implicated in response inhibition. Although an analysis of order effects is lacking in this and most other RTD studies, Clark et al. (2005) do provide a between-subject analysis of the first session only. This gives a near-significant difference in which the 18 tryptophan-depleted participants on average made more than twice as many discrimination errors as did the 22 participants given placebo. Future research could avoid problems associated with order effects or carry-over effects by employing parallel between-subject designs.

Research aiming to further uncover the synergic effects of novelty and reduced serotonergic neurotransmission, to separate these effects from learning effects, and to document which behavioral outcome measures are most sensitive to this phenomenon, might use a cross-over research design with four groups of the same gender. For two separate test days, each participant should be randomized into one of the following four groups:

1. Active depletion Test Day 1 and active depletion Test Day 2.
2. Active depletion Test Day 1 and placebo Test Day 2.

3. Placebo Test Day 1 and active depletion Test Day 2.
4. Placebo Test Day 1 and placebo Test Day 2.

Additionally, a novel task could be introduced on Test Day 2 using the design above, or in an ordinary cross-over design if this is unavoidable.

To our knowledge, this is the first study to investigate the role of novelty in relation to impulsivity and serotonergic neurotransmission. It is the first study to address this aspect directly and relate it to other RTD studies in which similar phenomena have been mentioned but never discussed. We hope this study will be relevant for researchers and clinicians experiencing anomalies in novel versus familiar tests and environments, especially in conditions where serotonin might be implicated. It is quite possible that the synergic effect between serotonin and novelty also applies to other aspects of behavior.

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