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Attention switching after dietary brain 5-HT challenge in high impulsive subjects

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Abstract

High levels of impulsivity have adverse effects on performance in cognitive tasks, particularly in those tasks that require high attention investment. Furthermore, both animal and human research has indicated that reduced brain serotonin (5-HT) function is associated with increases in impulsive behaviour or decreased inhibition ability, but the effects of 5-HT challenge have not yet been investigated in subjects vulnerable to impulsivity.

The present study aimed to investigate whether subjects with high trait impulsivity perform worse than low impulsive subjects in a task switching paradigm in which they have to rapidly shift their attention between two response rules, and to investigate the influence of a 5-HT enhancing diet. Healthy subjects with high ($n = 19$) and low ($n = 18$) trait impulsivity scores participated in a double-blind placebo-controlled study. All subjects performed the attention switch task in the morning following breakfast containing either tryptophan-rich alpha-lactalbumin (4.8 g/100 g TRP) or placebo protein (1.4 g/100 g TRP).

Whereas there were no baseline differences between high and low impulsive subjects in task switching abilities, high impulsive subjects made significantly more switch errors and responded slower after dietary 5-HT stimulation, whereas no dietary effects were found on task switching performance in low-impulsive subjects. The deterioration in task switching performance induced by the 5-HT enhancing diet in high impulsive subjects was suggested to be established by general arousal/attention-reducing effects of 5-HT, which might have a larger impact in high impulsive subjects due to either different brain circuitry involved in task switching in this group or lower baseline arousal levels.

Keywords

impulsivity, task-switching, response inhibition, Tryptophan, 5-HT

Introduction

Many psychiatric and psychopathological disorders, ranging from violent and antisocial behavioural disorders to eating disorders and Attention Deficit Hyperactivity Disorder (ADHD), have been related to poor response control or high levels of impulsivity (Evenden, 1999; Fadda, 2000; Fessler, 2002). Impulsive behaviour is often characterized by acting on a moment-to-moment basis without foresight and without considering adverse consequences before acting. Often, such behaviour can result in frequent aggressive encounters, bouts of drug or alcohol abuse, or poor concentration and impaired performance in cognitive tasks.

Even though impulsivity has been frequently studied, the biological mechanisms involved are still not fully understood. Among the multiple neurotransmitters that appear to be involved in the control of impulsive behaviour (Evenden, 1999), a reduced brain serotonin (5-HT) function seems to promote impulsive behaviour (Soubrie, 1986; Depue and Spoont, 1986), and enhanced 5-HT functioning is thought to go together with increased inhibition of behavioural responses (Asberg *et al*., 1976; Soubrie, 1986; Zametkin and Rapoport, 1987; Crean *et al*., 2002). First indications for links between 5-HT and impulsivity came from studies including clinical groups with impaired impulse control; these studies showed that low levels of brain 5-HT metabolites in cerebrospinal fluid correlated with impulsive, violent, and self-destructive behaviour (Asberg *et al*., 1976; Linnoila *et al*., 1983; see also Evenden, 1999). Further support for a relation between 5-HT dysfunction and impulsive behaviour was obtained from studies in which brain 5-HT was pharmacologically manipulated. These studies revealed either improved impulse control after intake of the 5-HT enhancing drug d,l-fenfluramine in criminals with a history of conduct disorders (Cherek and Lane, 2000) or impaired impulse control after 5-HT depletion in subjects with a vulnerability for alcoholism (LeMarquand *et al*., 1999; Crean *et al*., 2002).

As opposed to evidence for the relationship between brain 5-HT and impulsivity in clinical subjects, evidence for the involvement

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of brain 5-HT in behavioural control in healthy subjects appears to be sparse and inconsistent. Several researchers manipulated (decreased) brain 5-HT levels in healthy subjects by application of the acute brain tryptophan depletion method. Such studies reported either increased impulsivity (Walderhaug *et al*., 2002), diminished impulsivity (Crean *et al*., 2002), or no effect at all (Murphy *et al*., 2002; Clark *et al*., 2005; Cools *et al*., 2005). It is very likely, however, that such inconsistencies between studies on 5-HT and impulsivity might be explained by the different ways in which impulsivity is defined or artificially manipulated and by not taking into account trait impulsivity as a between-subjects factor.

Impulsivity research is complicated by the fact that impulsivity is a multifactorial phenomenon and specific aspects of impulsive behaviour may differ depending on individual differences as well as on the kind of neuropsychological test used to manipulate or measure impulsivity or impulsive behaviour. On the one hand, there are strong individual differences in trait vulnerability for impulsiveness that can be measured by self-report inventories like the Barratt Impulsivity Scale (Barratt, 1965) or the Impulsive subscale of the Eysenck Personality Inventory (EPI). In general, the assumption is made that subjects with high trait impulsivity will respond more impulsively and less accurately in cognitive tasks. In fact, such differences in behavioural control and cognitive performance between high and low impulsive subjects have often been demonstrated in behavioural or epidemiological studies (see McCown, 1993) and have been attributed to either differences in cortical arousal (Revelle *et al*., 1980; Eysenck and Eysenck, 1985) or dissimilarities in attention allocation abilities (Dickman, 1993). In light of such links between 5-HT and impulsive behaviour on the one hand and trait impulsivity and decreased cognitive performance on the other hand, it is surprising that between-subjects differences in trait vulnerability are seldom included in brain 5-HT manipulating studies. To our knowledge there are only a few studies that have investigated relations between trait impulsivity and cognitive performance in paradigms requiring inhibition or goal-directed behaviour (Clark *et al*., 2005; Cools *et al*., 2005). In these studies, conclusions were based on the computation of correlations between performance on the cognitive tasks and self-report BIS ratings of healthy subjects that were not selected for being either high or low impulsive, but rather appeared to have BIS scores in the normal range.

Besides trait impulsivity, impulsive behaviour may be defined on the basis of performance in certain cognitive tasks. In the impulsivity literature, different tasks have been used to report on distinct and often unrelated aspects of impulsive behaviour, ranging from impulsive planning (making impulsive decisions or choices, often based on punishing or rewarding feedback) to impulsive responding (as reflected by enhanced false alarms or reduced response inhibition abilities). Such different aspects of impulsivity appear to have different sensitivities to brain 5-HT manipulations. For instance, Winstanley *et al*. (2004) recently showed that, in rats, reduced brain 5-HT function (by means of 5-HT lesion with the serotonergic neurotoxin 5,7-DHT) had a specific effect on planning by strengthening the effects of response contingencies but did not influence response inhibition abilities. Furthermore, it might be the case that when 5-HT manipulations have no influence on task performance, they have an effect on underlying brain function. Rubia *et al*. (2005) recently showed that tryptophan depletion did not have an influence on the inhibition performance of healthy subjects in a Go/NoGo task, whereas it reduced right-inferior prefrontal activation in the NoGo-condition. In this respect, studies focusing on links between trait impulsivity and performance during tasks that require response inhibition (Go/NoGo and stop signal tasks) clearly show differences between clinical and non-clinical impulsive subjects. On the one hand, there is extensive evidence that ADHD subjects (children as well as adults) with combined impulsivity and inattention disorders have response inhibition problems and are less flexible in attention allocation in interference or switch tasks (Cepeda *et al*., 2000; Jonkman *et al*., 1999; Nigg *et al*., 2002; Bekker *et al*., 2005). In addition to the leading 'hyperdopaminergic hypothesis' of ADHD, there is some evidence for a modulating role of 5-HT in response inhibition and in the etiology of ADHD (Spivak *et al*., 1999), and clear interactions have been demonstrated between the dopamine and 5-HT systems in ADHD (Spoont, 1992; Quist and Kennedy, 2001). On the other hand, healthy (non-clinical) subjects with high scores on trait impulsivity scales like the BIS-11 or Eysenck's IVE do not show response inhibition difficulties in experimental tasks like the stop-signal task (SST) (Lijffijt *et al*., 2004). Furthermore, multiple studies indicate that pure response inhibition measures like stop signal reaction time (SSRT) are relatively insensitive to 5-HT manipulations (ATD) in healthy subjects (Clark *et al*., 2005; Cools *et al*., 2005).

Such inconsistencies between studies concerning clinical or non-clinical impulsives might however be related to the fact that frequently used response inhibition tasks like the stop-signal task or Go-NoGo tasks are not demanding enough and, thus, may not be sensitive enough to detect differences between healthy subjects with high or low trait impulsivity (Rubia *et al*., 2005). In fact, in a review, Dickman (1993) mainly reported differences between high and low (non-clinical) impulsives in cognitive tasks that pose high demands on attentional capacity, such as task switching performance. Task switching is a complex process and is measured by an increase in reaction time and errors when subjects have to switch from one task set to another, compared to when they have to generate the same response during subsequent trials. The last decade, a substantial body of research has aimed at identifying the different component processes and patterns of interference present during task switching (see Monsell, 2003 for a review). According to Allport and Wylie (2000), during task-switching stimulus-response associations play an important role; when a stimulus is presented, previous response-related information of that stimulus is retrieved. In case of inconsistent information, there is interference that slows down response selection, causing switch costs. Task switching thus involves both the inhibition of the previously relevant set/responses from working memory and the activation and selection of the currently relevant response set (Mayr and Keele, 2000). Schuch Koch (2003) presented evidence that suppression of the irrelevant task set takes place in the response selection stage. Task switching thus poses high demands on both the attention and inhibition systems, both in terms of capacity and flexibility. As a consequence of its relatively high attention demands, the task-switching paradigm may be particularly suitable to detect behavioural differences between healthy high and low impulsive-vulnerable subjects. Following

from previous findings, a first question to be asked is whether brain 5-HT manipulation has different effects on the task-switching performance of healthy subjects with varying levels of trait impulsivity. In addition, since acute tryptophan depletion has been found to increase impulsive behaviour, particularly in (sub)clinical subjects, it may be assumed that increasing brain 5-HT by dietary TRP challenge will have different effects on behavioural control performance in subjects with high and low trait impulsivity. This will be investigated in the present study.

In the present study, brain 5-HT will be manipulated by administration of a diet consisting of a protein component rich in alpha-lactalbumin. Alpha-lactalbumin (A-LAC) is a whey protein that contains the highest tryptophan content of all food protein sources (Heine *et al*., 1996). Since brain 5-HT is synthesized from the essential amino acid tryptophan, a rise in plasma concentration of the 5-HT precursor tryptophan (TRP) to the sum of the other large neutral amino acids (Trp/LNAA) gives tryptophan the advantage in competition for access into the brain (Fernstrom, 1990; Curzon, 1985). Recently, it has been demonstrated that a protein drink containing A-LAC causes a 50–70% (including 1.7 g TRP/100 g A-LAC) and even a 130% (including 4.8 g TRP/100 g A-LAC) increase in plasma TRP/LNAA (Markus *et al*., 2000, 2005; Orosco *et al*., 2004; Booij *et al*., 2006; Merens *et al*., 2005), thereby improving brain 5-HT function (Markus *et al*., 2000; Orosco *et al*., 2004) and cognitive performance (Markus *et al*., 2002).

In conclusion, the present study aims to investigate whether subjects with high trait impulsivity perform worse than low impulsive subjects in a task-switching paradigm and to investigate the influence of a 5-HT enhancing diet. The attention switching task used in the present study is adopted from earlier work in which differences in task switching abilities were demonstrated between children with or without ADHD, and between healthy adults and elderly people (Cepeda *et al*., 2000; Kramer *et al*., 1999). The expectation of worse task-switching performance in high impulsive subjects is based on studies showing that 1) subjects suffering from clinical disorders characterized by high impulsivity have worse attention switching and inhibitory abilities (Cepeda *et al*., 2000; Jonkman *et al*., 1999; Nigg *et al*., 2002; Bekker *et al*., 2005) and 2) high impulsives especially fail on attention demanding tasks (Dickman, 2003). In the presently used switch task, demands on task set inhibition were further enhanced by manipulating response compatibility so that half of the responses (in switch- and non-switch trials) required a response being incompatible with the stimulus. These modifications are found to place a 'higher burden' on task set inhibition processes (Kramer *et al*., 1999; Schuch and Koch, 2003). In addition, based on findings that acute TRP depletion reduces behavioural inhibition, a second question to be asked is whether dietary TRP challenge may improve behavioural control differently in healthy subjects with or without a vulnerability for impulsivity. To test these hypotheses, healthy subjects with high and low scores on the BIS-11 participated in a double blind, placebo-controlled study, in which they performed the switch task after either receiving a diet containing TRP-enriched protein or placebo protein.

Methods

Subjects

Dutch University students ($n = 235$) filled out the Barratt Impulsivity Scale (BIS-11) and a questionnaire package concerning personal details on eating habits and psychological and medical health status. From the highest quartile of the BIS score, 18 subjects (six men and 12 women) were selected for the high impulsivity group (BIS 75 ± 6) and from the lowest quartile of the BIS score 19 subjects (six men and 13 women) were selected for the low impulsivity group (BIS 49 ± 4). Exclusion criteria for participation were chronic and current illness, history of psychiatric or medical illness, medication use, irregular diets or deviant eating habits, excessive use of alcohol, cigarettes, coffee and/or drugs, allergy to milk products, and pregnancy as assessed by health and life-style questionnaires. All subjects participating in the experiment had a body mass index (BMI in kg/m^2) in the normal range between 20–25. All subjects participating the experiment were non-smokers and were not allowed to drink alcohol or to use any kind of drugs for two days before and during the experiment. The study was approved by the Local Ethics Committee of Psychology (ECP), University Maastricht and complied with the requirements of the European Council of Good Clinical Practice (GCP) adopted by the 52nd World Medical Association General Assembly, Edinburgh, Scotland (October, 2000). All subjects gave their informed consent to participate in the experiment and were paid for participation.

Procedure

The experimental procedure was conducted according to a double blind, placebo-controlled cross-over design and data-analysis was conducted without knowledge of subject's assignment and dietary condition. During two experimental sessions, subjects with high and low impulsivity scores were tested for task switching at the laboratory, following either a breakfast containing tryptophan-rich alpha-lactalbumin protein (A-LAC) or standard protein (placebo). The breakfasts were iso-energetic and contained equal amounts of protein, carbohydrate and fat. The order of presentation of the A-LAC and Placebo breakfast was counterbalanced between subjects; they were randomized to receive either the A-LAC or placebo protein first and than, after a period of 2 weeks, crossed over to the other dietary condition. An illustration of the design of the experiment is given in Figure 1.

On both experimental days, experimental sessions started at either 0830, 0915 or 1000 h, employing the same day and time within subjects. Subjects received written instructions, and were reminded again by a phone-call the day before arrival, not to eat anything approximately 12 h before the start of the experiment (except for water and tea without sugar). Immediately after their arrival, the procedure of the study was explained to the subjects and then a breakfast was consumed including either the A-LAC or placebo milkshake. Then they could relax or study in a waiting room for 1.5 h (they were encouraged to read). Then, subjects were brought into separated laboratory rooms and completed a computerized switch task.

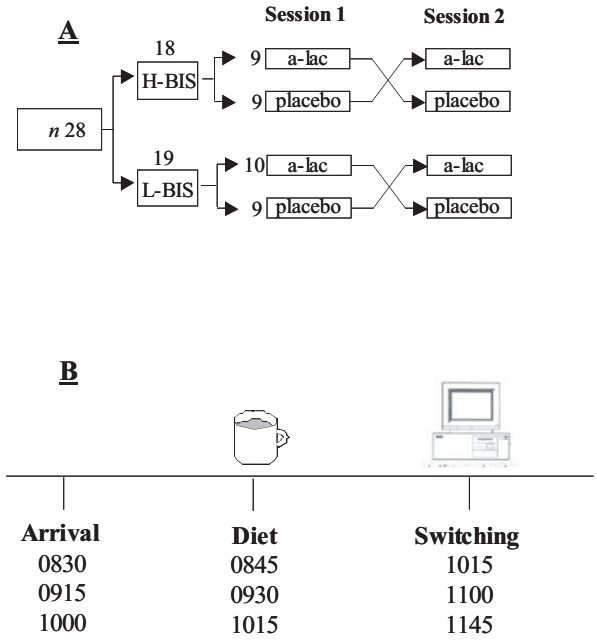

Figure 1 General design and time schedule of the experiment. (A) During two experimental sessions, subjects with high trait impulsivity (H-BIS; $n = 18$) and low trait impulsivity (L-BIS; $n = 19$) were monitored for task-switching performance following intake of a TRP-rich alpha-lactalbumin (A-LAC) diet and a TRP-low casein (placebo) diet. The order of presentation of the diets was counterbalanced within each subject group. (B) during each experimental session, subjects received the diets 15 min after arrival (three subjects each day). One and a half hour after dietary intake, task-switching performance was measured.

Diets

In order to manipulate brain 5-HT, the diet procedure was adopted from studies of Markus *et al*. (2000, 2005). On both experimental mornings, subjects received a breakfast consisting of two crackers with jam and a milkshake. The two dietary conditions were similar with the exception of the milkshake, in which the protein sources differed. The milkshake of the experimental diet (A-LAC) contained 20 g Trp-enriched (4.8 g/100 g Trp) alpha-lactalbumin protein (Davisco Foods International, Minnesota, USA) and the milkshake of the placebo contained 20 g (1.4 g/100 g Trp) sodium-caseinate (DMV International, Veghel, The Netherlands). The milkshakes were prepared by mixing the alpha-lactalbumin or placebo protein powder with 7 g chocolate milkshake-mix (Nesquik; Nestlé, Vevey, Switzerland) and 200 ml of water. The experimenter supervised dietary intake to make sure that all foods were consumed within 15 min. The amino acid profile of protein sources and the nutrient composition of the milkshakes are given in Table 1. In previous studies, comparable dietary manipulations were found to cause a 50–130% increase in brain TRP availability and brain 5-HT activity (Markus *et al*., 2000, 2005; Orosco *et al*., 2004; Booij *et al*., 2006; Merens *et al*., 2005).

Table 1 Composition of the amino acid profile of the tryptophan-rich milkshake (A-LAC) and the tryptophan-poor milkshake (Placebo) (adapted from Markus *et al*., AJCN, 2005)

	A-LAC	Placebo
Nutrient (g)		
Alph-lactalbumin protein	20	0
Sodium caseinate protein	0	20
Fruit aroma powder	7	7
Water	200	200
Amino acid profile (g/100 g		
Isoleucine	6.0	5.8
Leucine	10.8	10.1
Phenylalanine	4.1	5.4
Tyrosine	4.4	5.8
Valine	4.3	7.5
Tryptophan	4.8	1.4
TRP/LNAA ratio	1.7	0.4

Measurements

Barratt Impulsivity Scale (BIS-11) The BIS-11 is a 30-item self-report questionnaire, designed to measure impulsivity. All items were answered on a four-point Likert scale, ranging from 1 (rarely/never) to 4 (almost always/always). The minimum obtainable score is 30 (not impulsive) and the maximum score is 120 (extremely impulsive). The BIS is a generally accepted and frequently used valid measurement of trait impulsivity with a high internal consistency across populations (Patton *et al*., 1995). In the present study, the BIS was offered as a paper and pencil test.

Experimental attention switch task A computerized cognitive switch task was used to measure the subjects' capability to frequently switch their attention between different task instructions. This task was an adapted version of the task reported by Cepeda *et al*. (2000).

The task consists of three separate blocks of trials, two non-switch blocks and one switch block. Two response buttons were available to the subjects. During the task, four stimulus types (1, 3, 111 or 333) were randomly presented on the screen; either preceded by the task-set 'What number?' (subjects should press left when the cue '1' or '111' appeared and right when the cue '3' or '333' appeared), or 'How many?' (subjects should press left when the cue '1' or '3' appeared and right when the cue '111' or '333' appeared). In the first two non-switch blocks only one task-set was given, either 'What number?' or 'How many?', whereas during the last switch block both task-sets were randomly mixed. The two non-switch blocks contained 40 experimental trials each, consisting of 10 stimuli of each category ('111', '333', '1' or '3'). The switch block contained 80 experimental trials, 20 stimuli from each

category ('111', '333', '1' or '3'). Each trial consisted of a 400 ms task-set presentation, after which a stimulus was presented for 800 ms. After this, a 2000 ms response interval occurred, after which the next instruction appeared. All trails in each block were randomly presented to prevent predictability. Total time to complete the experimental task was about 20–30 min. Mean non-switch reaction time (RT) and number of errors was computed by averaging them over the first two non-switch blocks. Mean switch RT and number of switch errors were obtained by averaging RT and errors over switch trials in block 3.

Statistical analysis

The main research question formulated in the introduction was analysed by means of repeated measures univariate analyses of variance (ANOVA) by using the General Linear Model (GLM: SPSS 7.5 for Windows, SPSS Inc., Chicago) with one between-subjects factor *Impulsivity* (high versus low scores on the BIS; as independent variables) and two within-subjects factors *Diet* (A-LAC versus placebo as experimental manipulation) and *Switch* (mean RT and errors during the non-switch blocks versus the switch block; as dependent variables). Although we counterbalanced for the order of dietary manipulation effects (A-LAC first followed by placebo, versus the opposite order), the order of diet was preliminarily taken as a between-subjects factor. Yet, because order of diets did not contribute to any of the results, final analyses were performed with only *Impulsivity* as a between-subjects factor. Significant results revealed by these procedures were further examined by *post-hoc* univariate *t*-tests. All statistics were evaluated at a significance level of 5%. Data is reported as means ± SD.

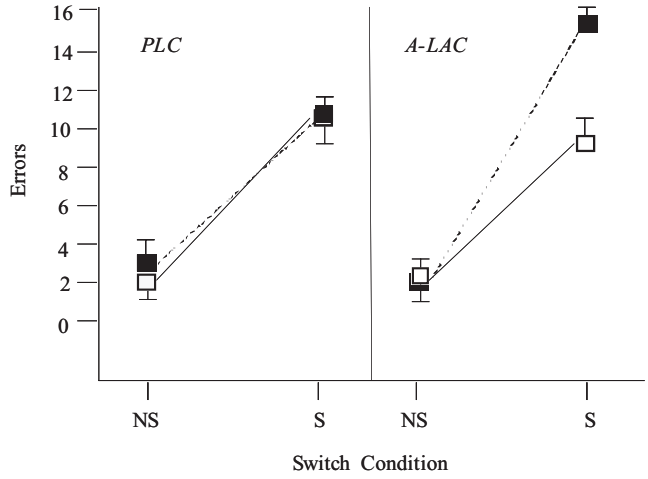

Figure 2 Mean changes in the number of errors during task switching (S) and non-switching (NS) one and a half hour after intake of a TRP-rich alpha-lactalbumin diet (A-LAC) and a TRP-low casein (placebo) diet in subjects with high (■) and low trait impulsivity (□). Repeated measures ANOVA revealed a main significant effect of *Switch* ($p < 0.0001$) and a significant three-way interaction effect of *Impulsivity* × *Diet* × *Switch* ($p < 0.001$). All subjects made significantly more errors during task switching as compared with non-switching (effect of *Switch*). In high impulsive subjects (■), this increase in the number of errors during switching was significantly increased after A-LAC, whereas there were no dietary effects in low impulsive subjects (□) (effect of *Impulsivity* × *Diet* × *Switch*).

Results

Task switching

A first repeated measures analysis with *Impulsivity* (high versus low impulsivity) as a between-subjects factor and *Switch* (switch versus non-switch) and *Diet* (A-LAC versus placebo) as within-subject factors was performed on the number of errors. Analysis revealed a main effect of *Switch* on the number of errors [$F(1,35) = 81.08$; $p < 0.0001$], indicating that in the switch condition significant more errors were made than in the non-switch condition. Analysis further revealed a significant interaction effect of *Impulsivity* × *Diet* × *Switch* [$F(1,35) = 12$; $p < 0.001$]; indicating significant differences in the effect of the switch manipulation on the number of errors between groups depending on dietary condition. As illustrated in Fig. 2, high impulsives made significantly more errors during switching as compared with non-switching after receiving A-LAC (versus placebo) [$T(18) = 2.36$; $p = 0.03$], whereas diet did not influence the number of switch errors in low impulsive subjects [$T(17) = -1.25$; $p = 0.23$].

A second repeated measures analysis with *Impulsivity* (high versus low impulsivity) as a between-subjects factor and *Switch* (switch versus non-switch) and *Diet* (A-LAC versus placebo) as within-subject factors was performed on reaction time. Analysis revealed a main effect of *Switch* [$F(1,35) = 179.9$; $p < 0.0001$]; indicating that reaction time increased during the switch condition as compared with the non-switch condition. Furthermore, the analysis revealed a near-significant effect of *Impulsivity* [$F(1,35) = 3.56$; $p = 0.067$], high impulsive subjects tended to have slower response times in both the non-switch and the switch condition. A significant interaction of *Diet* × *Impulsivity* [$F(1,35) = 4.16$; $p = 0.05$], indicated that reaction times in both switch and non-switch conditions slowed even more in high impulsive subjects after the A-LAC diet (mean 500 ± 71 ms) when compared with placebo (479 ± 70 ms), whereas there were no dietary effects in low impulsive subjects (454 ± 55 ms after A-LAC versus 457 ± 52 after placebo) (see Fig. 3).

Discussion

This study examined whether high impulsive subjects had better task-switching abilities than low impulsive subjects and whether such differences are sensitive to dietary brain serotonin (5-HT) manipulation. Dietary increases in brain 5-HT were found to impair task-switching performance only in high impulsive subjects.

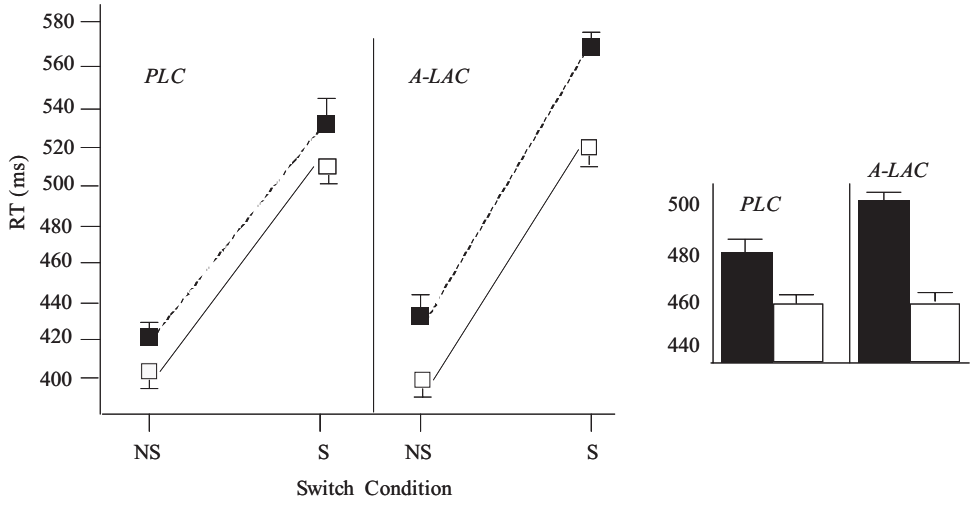

Figure 3 Mean changes in Reaction time (RT) during task switching (S) and non-switching (NS) one and a half hour after intake of a TRP-rich alpha-lactalbumin diet (A-LAC) and a TRP-low casein (placebo) diet in subjects with high (■) and low trait impulsivity (□). Repeated measures ANOVA revealed a main effect of *Switch* ($p < 0.0001$) and a two-way interaction effect of *Diet* × *Impulsivity* ($p < 0.05$). All subjects became significantly slower during task switching as compared with non-switching (effect of *Switch*). Only in high impulsive subjects (■), mean RT (in both switching and non-switching) became significantly slower after A-LAC as compared with placebo (effect of *Diet* × *Impulsivity*).

Dietary tryptophan manipulation of brain 5-HT

Although variations in plasma TRP/LNAA were not measured in the current study, 50–130% rises in plasma TRP/LNAA have been reported after comparable A-LAC intake in multiple studies from different research groups including different healthy and subclinical subjects (Markus *et al*., 2000, 2005; Orosco *et al*., 2004; Booij *et al*., 2006; Merens *et al*., 2005). Since a 40–50% increase in plasma TRP/LNAA is thought to cause meaningful changes in brain TRP and 5-HT (Fernstrom, 1990; Curzon *et al*., 1985; Markus *et al*., 2000), it seems justified to assume that after A-LAC more TRP was available for uptake into the brain.

Effects of trait impulsivity on task switching

The validity of the switch task was supported by a main switch effect, indicating slower reaction time and higher error rates during switching as compared to non-switching (also called switch costs). This is in agreement with previous data using a similar task (Cepeda *et al*., 2000, 2001; Kramer *et al*., 1999). In most task-switching paradigms, switch costs are thought to arise mainly from two processes: the difficulty to inhibit the previously relevant task set and the time needed to activate the currently relevant task set (Allport *et al*., 1994; Monsell, 2003). In the current switch task, demands on task set inhibition were further enhanced by including response incompatibility in half of the switch- and non-switch trials. This has been found to place an even higher burden on task set inhibition processes (Kramer *et al*., 1999; Schuch and Koch, 2003). However, due to the relatively low number of trials it was not possible to split up switch costs for response compatible and response incompatible trials. Assuming that this switch task is more sensitive for detecting differences in non-clinical impulsives (see Introduction), a first salient observation is the absence of performance differences in the placebo condition between high and low BIS responders. Although an almost significant main *Impulsivity* effect ($p < 0.07$) indicated that high impulsives tended to respond more slowly than low impulsive subjects, this was not specific for the switch condition. The absence of baseline differences between the groups may be due to the relatively small distiction in high and low BIS scores. Such relatively small differences in scores between the groups might be caused by the fact that these groups were formed out of a student population of 235 subjects in which impulsivity problems are less represented than in the general population. Nevertheless, the significant interactions involving Impulsivity and Diet, which will be elaborated on in the following section, indicate that apparently small variations in impulsivity scores are sufficient enough to discriminate between the effects of 5-HT manipulation.

Effects of dietary 5-HT manipulation on task switching and impulsivity

The A-LAC diet had significant effects on task performance depending on impulsivity. High impulsive subjects made relatively more switch errors and showed slower response patterns after A-LAC as compared to placebo, whereas no diet effects were found in low impulsive subjects. 5-HT challenge was predicted to improve performance on the current switch task, which requires

inhibition and attentional flexibility, particularly in subjects with high impulsivity. This hypothesis was based on previous findings of reduced brain 5-HT function in impulsivity and studies reporting that 5-HT depletion led to an *increase* in impulsive responding in healthy subjects (Waldenhaug *et al*., 2002). Links between lower brain 5-HT levels and *increases in* impulsive behaviour (or worse inhibition) were further suggested by pharmacological studies (Cherek and Lane, 2000), revealing either reduced impulsive behaviour after the 5-HT releasing drug d,l-fenfluramine (Cherek and Lane, 2000) or increased impulsive behaviour after 5-HT depletion (Cools *et al*., 2005). Contrary to our hypothesis, the present results reveal that task-switching behaviour is negatively influenced by tryptophan challenge only in those subjects with high trait impulsivity. Whereas this negative influence on task-switching performance was not expected at first, it is congruent with the assumed general inhibitory influence of 5-HT on motor actions and on information processing in general (Spoont, 1992). Considering such assumed inhibitory influences of 5-HT, enhancements in 5-HT would improve motor inhibition but at the same time would have a negative effect on the amount of information that can be processed or distributed at one particular time, leading to a deterioration in tasks requiring rapid shifts of attention between stimuli or task sets, such as switch tasks. In fact, several studies support such a hypothesis by showing that reduced 5-HT levels after ATD or 5-HT antagonists were associated with improved performance in tasks requiring frequent attention shifts (Hatcher *et al*., 2005) but impairments in performance in response inhibition tasks (LeMarquand *et al*., 1999; Crean *et al*., 2002). Still, there remain many inconsistencies between studies on the effects of 5-HT on inhibition or task switching performance. Another explanation for these inconsistencies might be sought in differences between the tasks used in the different studies. As discussed earlier, different cognitive tasks target different aspects of impulsive behaviour or inhibition and hence require the recruitment and activation of different brain circuits (Evenden, 1999; Winstanley *et al*., 2004; 2006) that might be more or less dependent on brain 5-HT neurotransmission. Furthermore, effects of 5-HT manipulation might not always become evident in behavioural performance in the task when the task does not have a high difficulty level. Rubia *et al*. (2005), for instance, showed that whereas healthy subjects' inhibition performance in a Go/Nogo task was not influenced by tryptophan depletion, it did reduce brain activation in the right orbito-inferior prefrontal cortex and enhanced general activation in the superior and medial temporal cortices. According to the authors, this increased engagement of temporal brain regions may reflect compensatory mechanisms.

The fact that the negative effect of 5-HT challenge on task switching only appeared in high impulsive subjects might also be explained by recruitment of different brain areas during task performance that particularly in these vulnerable subjects have become differentially sensitive to 5-HT manipulations. The present study cannot confirm such an explanation in impulsive-vulnerable subjects, but a recent fMRI study by Horn *et al*. (2003) showed that in healthy subjects, high scores on trait impulsivity scales were associated with enhanced inaccuracy levels in a Go/Nogo task (reduced inhibition) and greater activation of paralimbic areas, whereas individuals with lower scores activated higher order association areas. Another explanation might be sought in the lower basal arousal levels assumed to be present in extravert or high impulsive subjects (Eysenck and Eysenck, 1985). Such lower arousal levels might underlie the generally slower response patterns in both switch and non-switch conditions in high impulsive subjects in the present study. Lower baseline arousal levels might cause high impulsives to experience even larger attention 'dampening' effects after TRP enhancement, which is assumed to cause an even larger effect on attention demanding tasks.

In conclusion, the findings from the present study show once more that the role of the 5-HT system in impulsivity is far more complex than often envisaged and strongly suggest that 5-HT may influence different facets of impulsivity in independent ways depending on task paradigms as well as on individual differences in trait impulsivity. It is hypothesized that the deterioration in task-switching performance in high-impulsive subjects after intake of the TRP-enhancing diet in the present study is caused by the inhibitory effect of 5-HT on attention flexibility, or the amount of attention that can be allocated to the task. Possible explanations for the presence of a diet effect on task switching performance only in healthy subjects with relatively high trait impulsivity scores might be sought in the activation of different brain networks with varying 5-HT sensitivty or in lower baseline arousal levels in this group. Future research is, however, needed to corroborate such hypotheses and to explore whether this effect generalizes to clinical populations with attentional disorders. Furthermore, it would be important to study such effects in healthy subjects with different types of trait impulsivity, such as motor impulsiveness versus attention impulsiveness as distinguished in the BIS-11 (Patton *et al*., 1995).

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