BMC Psychiatry

Research article

Effects of acute tryptophan depletion on executive function in healthy male volunteers

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Abstract

Background: Neurocognitive impairment is frequently described in a number of psychiatric disorders and may be a direct consequence of serotonergic dysfunction. As impairments in executive functions are some of the most frequently described, the purpose of this study was to examine the performance of normal volunteers on a range of executive tasks following a transient reduction of central serotonin (5-HT) levels using the method of acute tryptophan depletion (ATD).

Methods: Fifteen healthy male subjects participated in a within-subject, double-blind, counterbalanced crossover study. ATD was induced by ingestion of a 100 g amino-acid drink. Executive function was evaluated using the Wisconsin Card Sorting Test, Stroop, Verbal Fluency and Trail Making. Visual analogue scales were administered to assess mood.

Results: Plasma free and total tryptophan concentrations were significantly reduced by the depleting drink ($P < 0.001$). ATD selectively improved motor speed/ attention on the Trails A test ($P = 0.027$), with no effect on subjective ratings of mood. Interaction effects between drink and the order of drink administration were observed on most neurocognitive tests.

Conclusions: The improvement in simple motor speed/ attention following ATD is in keeping with the ascribed role of 5-HT in the cortex, however performance on tests of executive function is not robustly altered. The presence of interaction effects on most tasks suggests that subtle changes may occur but are masked, possibly by simple learning effects, in the context of a crossover design. This has implications for the design of future studies, particularly those examining executive functions.

Background

Serotonin (5-hydroxytryptamine; 5-HT) systems are widely distributed throughout the central nervous system.

The existence of specific pathways projecting from the raphé nuclei to the forebrain and the density of 5-HT receptors in these and other areas, such as the

hippocampus, amygdala and cortex, supports the growing body of evidence implicating 5-HT in the processes of learning and memory [1,2].

Interest has focused on the serotonergic system not only because of its ascribed role in normal neurocognitive functioning, but because of the implication that 5-HT systems may be compromised in many psychiatric disorders [3] including, schizophrenia [4], bipolar disorder [5] and major depression [6]. It has been established that neurocognitive impairment is a core feature of these disorders [7–9] and this may, in part, be a consequence of serotonergic dysfunction.

While the pattern and magnitude of impairment in these disorders is diverse and dependent upon many factors, including clinical state at the time of testing, previous studies have frequently reported impairments in executive functioning [10–12]. Executive functions are 'higher-order' cognitive processes involved in planning, judgement, decision-making, anticipation or reasoning, and are responsible for the control of attention, inhibition, set-shifting and task management [13]. The neuroanatomical locus of these processes is considered to be the frontal lobes, specifically the prefrontal cortex, which over time, has become synonymous with executive functioning itself. However, it is now understood that such processes activate diverse neural circuitry forming reciprocal frontal-subcortical loops [14] and therefore that executive functions are linked to, but not coterminous with, the operation of the frontal lobes [15,16]. Nevertheless, the known innervation of 5-HT pathways to these sites suggests that executive functions may be dependant upon the integrity of the serotonergic system.

The precise role of the serotonergic system in cognition is complex. Recent studies have suggested that a previously proposed dichotomy – that stimulation of the 5-HT system impairs learning and memory, whereas a reduction in serotonergic function may enhance these processes – requires reformulation as $5-HT_{1A}$, $5-HT_{2A}$, $5-HT_{2C/2B}$ and $5-HT_4$ receptor antagonists do not consistently alter learning and memory in animals [17]. However, it is not clear how reliably this can be translated to humans. Impairments in spatial working memory have been demonstrated following administration of the 5-HT agonist, fenfluramine [18], and in list-learning following administration of the partial $5-HT_{1A}$ receptor agonist, buspirone, accompanied by changes in regional cerebral blood flow [19]. Clomipramine, a non-selective serotonin reuptake inhibitor, has been shown to impair memory in patients with depression [20] and panic disorder [21], however this may be attributable to anti-cholinergic effects. In some studies, single doses of SSRIs have been shown to improve performance on choice reaction time tasks in

normal volunteers [22–24], although some of these effects may occur though indirect actions involving other neurotransmitter systems [25]. Alternatively, acute administration of an SSRI through activation of pre-synaptic $5-HT_{1A}$ receptors may result in a net reduction in serotonergic neurotransmission.

An alternative means of examining serotonergic involvement in cognition is by selectively decreasing brain 5-HT levels by the method of tryptophan depletion [26]. Acute tryptophan depletion (ATD) using an amino acid drink leads to around an 80 % depletion of plasma total and free tryptophan (TRP), resulting in a moderate but significant reduction of central 5-HT metabolism [27]. We have previously found impairments in executive function in schizophrenia following ATD. Specifically, on the Wisconsin Card Sorting Test, ATD led to a significant reduction in the number of categories completed but only when the task is novel i.e. on the first visit. Tests of learning and memory were unaffected [28].

In healthy volunteers the effects of ATD on executive functions are not consistent. Park et al [29] found no evidence directly implicating the 5-HT system in 'frontal lobe' functions. Schmitt and colleagues have suggested that long-term memory is impaired following ATD, while some executive functions may be enhanced, such as verbal fluency and focused attention [30]. ATD has been reported to alter decision making in executive tasks, but this may be the result of changes in impulsivity rather than an effect on planning *per se* [31,32]. Other studies have failed to find effects of ATD on any aspect of neuropsychological function [33,34].

In the present study we sought to focus on the effects of ATD on the WCST and a range of other tests of executive function. Changes in subjective mood were also assessed. As insufficient depletion may have been a contributory factor in the lack of effects seen in our previous study [34] we employed a more potent 100 g amino-acid drink.

Methods
Subjects
All subjects were recruited as part of a larger study examining the effects of ATD on EEG and neurocognitive function. The results of the EEG component of the study are reported elsewhere [35]. Fifteen healthy male volunteers, aged between 18 and 25 years (mean = 22.4, SD = 1.9 years) with a NART estimated IQ (National Adult Reading Test; [36]) of between 90 and 118 (mean = 109, SD = 7.9) and 14 to 19 years of education (mean = 16.7, SD = 1.8 years) participated in the study. All subjects were paid for their participation. After full description of the study, written informed consent was obtained. The study received full approval from the local ethics committee.

Experimental Design

A within subject, double-blind, cross-over study was used. Subjects attended the research unit at 0830 h following an overnight fast and underwent baseline assessments. A 100 g amino acid drink was then administered. Subjects received either the depleting or the control drink. Blood samples for free and total TRP were taken at baseline and 5 hours after ATD or control drink. Between 6 and 7 hours after consumption of the amino-acid drink, neuropsychological testing was carried out. After a minimum two-week washout period, subjects returned for repeat testing with the alternative drink. Nine subjects received the depleting drink on their first visit, and 6 the control drink.

Drink Composition

Both drinks were of identical composition, with the exception of the addition of 2.3 g of L-tryptophan to the control drink. A 100 g amino acid drink was used [28,37], the constituents being L-alanine 5.5 g, L-arginine 4.9 g, L-cysteine 2.7 g, L-glycine 3.2 g, L-histidine 3.2 g, L-isoleucine 8 g, L-leucine 13.5 g, L-lysine monohydrochloride 11 g, L-methionine 3 g, L-phenylalanine 5.7 g, L-proline 12.2 g, L-serine 6.9 g, L-threonine 6.5 g, L-tyrosine 6.9 g, L-valine 8.9 g. This was mixed in 300 ml water, flavoured with blackcurrant and sweetened with saccharin.

Biochemical Measures

Ten millilitres venous blood was taken on two separate occasions during each experimental session. The blood was added to anticoagulant and the plasma was immediately separated by centrifugation. A sample for free tryptophan was further centrifuged using an ultra-filtrate tube. All samples were stored at -20°C until assay. Plasma total and free tryptophan was determined by High Pressure Liquid Chromatography by the method of Marshall et al [38].

Subjective Mood Ratings

Subjective rating of mood was assessed using visual analogue scales (VAS). The 16 scales used in the present study condense into 3 factors: 'Alertness', 'Contentedness' and 'Calmness', which have been shown to be sensitive in the measurement of drug effects [39].

Neurocognitive assessment

The Wisconsin Card Sorting Test (WCST) (PAR Inc [40])

This computerised test requires the subject to sort a number of cards displaying either one, two, three or four; red, green, yellow or blue; triangles, stars, crosses or circles according to either number, colour, or shape of the symbols on the card. The subject is not told which parameter to sort by. After ten correct responses in a row, the sorting principle changes. Thus, while the cards must be sorted according to colour at the start of the test, the sorting principle changes to 'shape', then to 'number' as the test progresses. The test lasts until six blocks of ten correct matches have been made or until a maximum of 128 cards have been presented.

Verbal Fluency (Benton's FAS; [41])

This is a test of verbal fluency which is sensitive to frontal dysfunction [42]. There are 3 trials, each lasting 60 seconds, in which subjects are required to list as many words as possible, beginning with the given letters – 'F', 'A' and 'S' – excluding proper nouns or repetitions of the same word with a different suffix. Performance is assessed by the sum of acceptable words produced across the 3 trials.

Stroop Colour-Word Test [43]

This selective attention task is comprised of two trials. Trial "C" requires subjects to read aloud a list of 112 colour names in which no name is printed in its matching colour. In the subsequent "C-W" trial, subjects are required to name the colour of ink in which the colour names are printed. The colour-word score is considered a measure of inhibitory control. Time to complete each trial is recorded, and an interference index by subtracting trial C from CW.

Trail-Making Test [44]

This test of visuo-motor speed and attention requires subjects to join numbers in ascending order (part A), and then alternate between letters and numbers (part B). Scoring was the time (seconds) to complete each condition, and a shift index derived by subtracting the time taken to complete part A from part B.

Statistical Analysis

All descriptive statistics are presented as mean and standard deviation (SD). Changes in TRP levels were analysed using paired t-tests. All mood scales and neurocognitive tests were subjected to a mixed effects analysis of variance (ANOVA) with 'drink' (ATD or control) as a within subjects factor and 'order' of depletion (ATD first or control first) as a between subjects factor. Where the assumptions of the ANOVA were violated, data were subjected to logarithmic (base 10) transformations (i.e. verbal fluency). *Post hoc* analyses were carried out by *t*-test. The WCST could not be transformed satisfactorily to achieve normality, therefore main effects and any *post hoc* analyses of significant interactions were confirmed non-parametrically. All analyses were performed using SPSS version 9 [45].

Results

Tryptophan levels

Complete sets of plasma samples were not available for three subjects. As a result data are quoted from the remaining 12 subjects. Following ATD, plasma total (mean = 85.6, SD = 3.9%) and free (mean = 84.4, SD = 5.1%) tryptophan concentrations were significantly reduced ($P < 0.001$). Conversely, the control drink

Table 1: Descriptives and ANOVA results for all measures

| | ATD | | Placebo | | ANOVA results [†] | | |
	Mean	(SD)	Mean	(SD)	Drink	Order	Drink × Order
WCST [a]							
Categories completed	5.5	(1.4)	5.7	(0.8)	F = 0.019, P = 0.893	F = 0.019, P = 0.893	F = 3.161, P = 0.099
Trials to complete 1st category	12.0	(4.9)	13.6	(4.6)	F = 0.996, P = 0.336	F = 0.002, P = 0.966	F = 0.183, P = 0.676
Perseverative errors (%)	9.2	(4.4)	9.1	(3.2)	F = 0.112, P = 0.744	F = 1.457, P = 0.249	F = 4.712, P = 0.049 *
Non-perseverative errors (%)	9.8	(7.3)	8.3	(4.4)	F = 0.012, P = 0.887	F = 0.549, P = 0.472	F = 12.531, P = 0.004 ***
Conceptual level responses (%)	76.8	(16.1)	79.5	(9.7)	F = 0.004, P = 0.949	F = 0.902, P = 0.359	F = 7.947, P = 0.014 *
Verbal fluency							
Correct	43.2	(9.2)	44.2	(9.4)	F = 0.166, P = 0.690	F = 6.098, P = 0.028 *	F = 0.432, P = 0.522
Stroop							
C (latency; seconds)	54.1	(5.5)	54.1	(8.9)	F = 0.006, P = 0.940	F = 0.007, P = 0.934	F = 0.149, P = 0.706
CW (latency; seconds)	114.0	(16.7)	112.7	(14.8)	F = 0.049, P = 0.828	F = 0.079, P = 0.783	F = 11.560, P = 0.005 ***
Interference (CW – C)	59.9	(16.9)	58.7	(15.3)	F = 0.022, P = 0.883	F = 0.056, P = 0.816	F = 7.615, P = 0.016 *
Trail Making							
Trails A (seconds)	23.3	(5.0)	25.3	(6.5)	F = 6.232, P = 0.027 *	F = 0.021, P = 0.886	F = 8.680, P = 0.011 *
Trails B (seconds)	49.9	(10.4)	48.4	(9.4)	F = 0.109, P = 0.746	F = 3.272, P = 0.094	F = 1.999, P = 0.181
Shift index (Trails B – A)	26.7	(11.0)	23.1	(7.4)	F = 1.601, P = 0.228	F = 4.829, P = 0.047 *	F = 0.008, P = 0.928
VAS mood scale							
Alertness	74.0	(14.0)	71.4	(16.2)	F = 0.595, P = 0.454	F = 0.905, P = 0.359	F = 3.838, P = 0.072
Contentedness	83.4	(7.5)	86.5	(7.8)	F = 2.372, P = 0.147	F = 1.922, P = 0.189	F = 1.298, P = 0.275
Calmness	82.8	(12.2)	81.6	(16.4)	F = 0.014, P = 0.908	F = 0.854, P = 0.372	F = 0.570, P = 0.464

[†] degrees of freedom = 1,13 [a] Results confirmed non-parametrically; see main text.

increased total (mean = 64.7, SD = 51.8%) and free (mean = 71.3, SD = 57.9%) tryptophan concentrations (P = 0.001). These findings are in line with previous studies using a similar amino acid mixture [26].

Neurocognitive and mood measures
All results are presented in table 1.

There were no main effects of drink, order or interactions on any of the VAS sub-scales. In the case of the neurocognitive tests, the only main effect of drink was found on the Trails A test which was completed significantly faster following ATD. Main effects of order were present for verbal fluency and the Trails test shift-index, with the group receiving ATD first performing significantly better on both measures.

Interaction effects
Significant drink by order interactions were found on several measures: WCST, perseverative errors, non-perseverative errors and conceptual level responses; Stroop, colour-word latency and interference index; Trails A, latency (see Table 1).

On the WCST, *post hoc* analyses revealed that in the group who were depleted on the second visit, significantly fewer

perseverative (z = -2.060, P = 0.039) and non-perseverative (z = -2.023, P = 0.043) errors were committed, and greater conceptual level response attained (z = -2.032, P = 0.042) following ATD. The opposite pattern emerged in subjects depleted on their first visit, with non-perseverative errors being significantly lower following the control drink (z = -2.240, P = 0.025). Perseverative errors were also lower (z = -1.719, P = 0.086) and conceptual level responses higher (z = -1.334, P = 0.182) although these results did not reach statistical significance (see figure 1).

A similar overall pattern emerged in the interactions from the Stroop test. In subjects who were depleted on the second visit, latencies were significantly reduced for the 'CW' component (t = -2.712, df = 5, P = 0.042) and the interference index (t = -2.607, df = 5, P = 0.048) following ATD. In subjects who were depleted on the first visit, the 'CW' latency was significantly lower following the control drink (t = -2.333, df = 8, P = 0.048) although the difference in the interference index did not reach significance (t = -1.809, df = 8, P = 0.108) (See figure 2).

For the Trails A interaction, subjects who were depleted on their second visit completed the test significantly faster following ATD (t = -3.728, df = 5, P = 0.014), however there was no difference in performance between drinks in
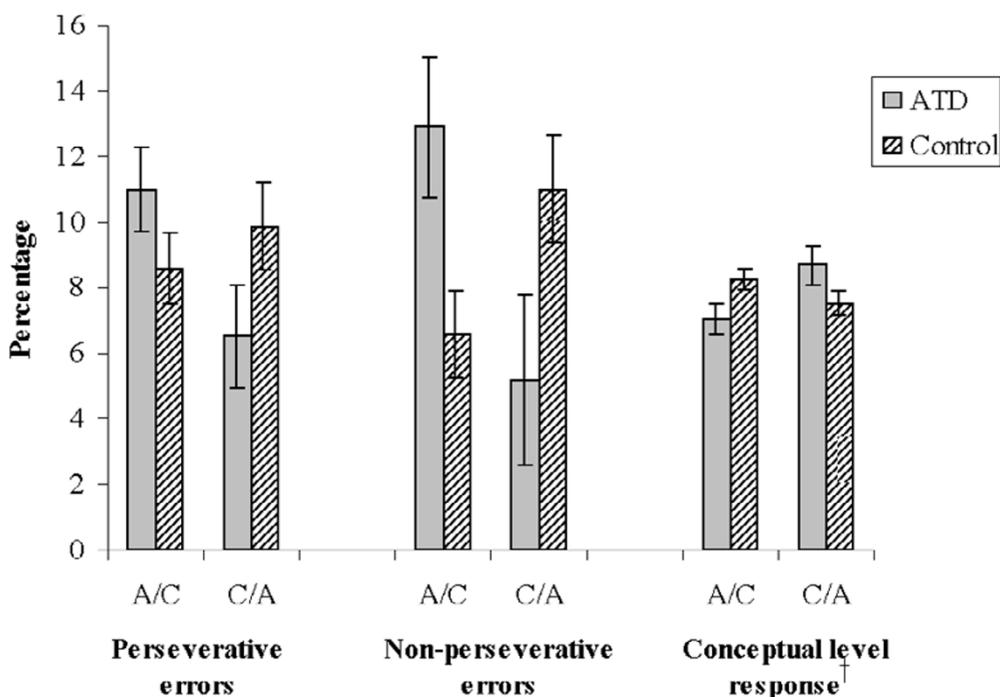
Figure 1
Drink by order interactions from the WCST Legend: A/C; Group receiving active first, control second. C/A; Group receiving control first, active second. †; Percentage (×10^1), nb. For this measure only, higher scores represent better performance.

subjects depleted on their first visit (t = -0.344, df = 8, P = 0.740) (see figure 3).

Discussion

In this study, the effects of ATD on executive function and subjective mood state were examined. Both free and total plasma TRP were significantly reduced by the depletion protocol, however no effect on mood was found. Of the neurocognitive tests, the only main effect of drink was found on the Trails A test, with latencies reduced by ATD compared to the control drink. Drink by order interactions were observed in outcome measures from all tests with the exception of verbal fluency.

In our previous study in healthy volunteers [34], we found no main effect of ATD on any measure of learning, memory or executive function. Inadequate depletion as a result of using a less potent but more tolerable 52 g amino-acid drink was suggested to be a possible contributory factor. A 100 g drink was used in the present study, but despite reducing tryptophan levels by around 85%, no effects were observed on any aspect of executive functioning other than an improvement in visuo-motor speed and attention (Trails A).

It has been suggested that the most accurate method of estimating centrally available tryptophan is by defining the percentage depletion as a ratio of tryptophan to other large neutral amino acids (TRP/LNAA ratio) [46]. Although LNAAs were not measured in the present study, our previous work has shown that the active 100 g amino-acid drink significantly decreases TRP/LNAA ratios, while this ratio remains unchanged following administration of the control drink, despite an increase in absolute tryptophan levels [28]. This protocol is also specific to 5-HT function. The ratio of tyrosine (the precursor of catecholamines) to other LNAAs does not change significantly with ingestion of either drink, and thereby excludes possible dopaminergic effects [28].

From the results of the present study it is clear that the most consistent finding is the presence of interaction effects in the majority of tests, although the interpretation of such effects is somewhat complex. The most parsimonious explanation is that the interaction represents a simple learning effect. As can be seen in figures 1 and 2, subjects receiving the depleting drink on visit 2 perform better when depleted, whereas those receiving the control drink on visit 2 are better following the control drink. In
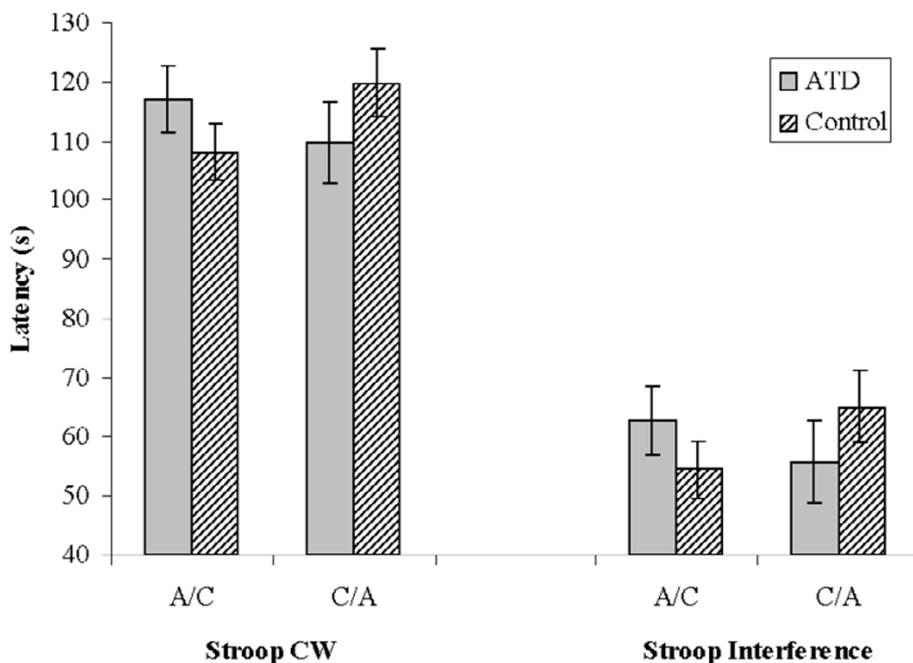
Figure 2
Drink by order interactions from the Stroop test
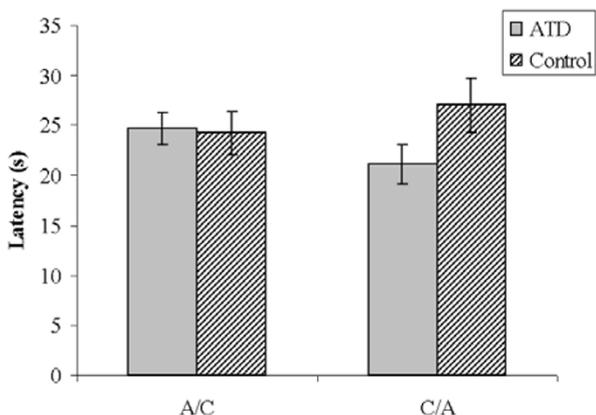
Figure 3
Drink by order interaction from the Trails (A) test

other words, there is an apparent improvement in performance on the second visit irrespective of the drink administered.

Alternatively, it is possible that 'genuine' effects of drink may be confounded by these learning effects, when present in the context of a crossover design. For example, when analysed *post hoc*, all 6 outcome measures on which significant interactions were observed showed significantly improved performance following ATD when administered on the second visit. However, in the group which received the control drink on their second visit, only 2 actually reached significance. This is especially clear in the interaction on the Trails A test (figure 3). Previous studies examining the effects of ATD on executive functions have suggested that attention may be improved when depleted, through the removal of inhibitory actions of 5-HT in the cortex [30,37]. Therefore, if ATD does improve this aspect of performance, the difference would be magnified in the group depleted on their second visit where the effects of ATD and task familiarity would combine. The opposite is also true and the effect would be markedly attenuated in the group depleted on visit 1 when the task is novel, and the result is compared to the 'learning effect' when the control drink is administered on visit 2.

The finding of an improvement in attentional performance (trails A) following ATD in the present study is in keeping with the literature and the role of 5-HT [47]. What

is more inconsistent are the effects on other executive functions, especially in contrast to effects on learning and memory. In their study Park et al [29] used a range of tests from the CANTAB, particularly executive and visuo-spatial memory and concluded that ATD elicited a deficit in retrieval processes. However, ATD has also been shown to impair episodic memory recall in the absence of changes in EEG neural correlates of retrieval in healthy subjects [35]. This suggests that ATD may affect specific stages of information processing, namely acquisition and/or consolidation. There is some support for this hypothesis, as effects have been demonstrated in other tests of long-term memory (LTM). Schmitt et al [30] reported impaired memory consolidation following ATD, but improved focused attention. Riedel et al [48] found ATD impaired several measures of long-term memory consolidation in the absence of retrieval effects. Importantly, this effect appeared to be highly specific and did not influence short-term or working memory, perceptual, attentional, psychomotor and executive functions. This would seem to suggest that the functioning of the hippocampus – which contains a high density of 5-HT receptors – and therefore the declarative memory system, is differentially sensitive to the acute depletion of 5-HT in healthy subjects.

Executive tasks such as the WCST (or the analogous ID/ED set-shift task from the CANTAB) and the Tower of London (TOL) test of planning have been utilised in several ATD studies with mixed results. Rogers et al [31] found impairments in ID/ED reversal shifts, while Park et al [29] reported order-dependant effects on the TOL. Our earlier study failed to find effects on any of these tasks [34], although we have found subtle effects in cohorts of patients with possible vulnerabilities of the serotonergic system [28,37]. There are several possible explanations for this:

Firstly, Robbins [49] has suggested that performance on these tasks is mediated by different neurotransmitter systems. Therefore manipulations affecting central catecholamine systems specifically affect certain tasks sensitive to dorsolateral prefrontal dysfunction (i.e. TOL), whereas tasks involving reversal shifts or decision making are dependant upon the integrity of the orbitofrontal cortex and are sensitive to indolamine manipulation. However, this dichotomy is not always present as can be seen in the studies discussed previously.

A second possibility is that even in 'healthy' subjects, some individuals may be particularly sensitive to the effect of ATD through risk factors such as a positive family history (FH+) of psychiatric disorder [For a review see, [47]]. Several studies have shown small reductions in mood following ATD in such individuals [50,51] although there are exceptions to this, particularly with

respect to neurocognitive functioning where several studies have failed to find differential effects in FH+ subjects [48] or in cohorts with a high proportion of FH+ [33]. This is especially problematic as studies of the effects of ATD tend to involve small sample sizes.

A final possibility returns to our earlier suggestion that disruption of 5-HT levels at the hippocampus may be central to the observable effects on neurocognitive function, even executive functions. Riedel et al [47] have speculated that memory consolidation impairment is mediated by the inhibiting effects of ATD on temporal regions, especially the hippocampus, whereas the improved attentional performance is mediated by enhanced fronto-cortical arousal. However, as stated earlier, there are a multiplicity of processes subserved by the central executive [13] the functioning of which is linked to, but not necessarily coterminous with, the operation of the frontal lobes [15,16]. Executive functions activate diverse neural circuitry forming reciprocal frontal-subcortical loops stemming from structures such as the basal ganglia and hippocampus, projecting forward to the frontal lobes [14]. Animal studies have confirmed that tryptophan depletion reduces 5-HT levels in frontal cortex [52], hippocampus and striatum [53] as well as total brain levels [54]. Therefore (executive) tasks which rely upon the integrity of these circuits are likely to be affected differentially by ATD depending upon the specific demands of the task and possibly the particular outcome measures derived. For example, increased frontal arousal and inhibition at posterior sites may result in increased speed of response, but with decreased accuracy, especially with complex tasks. This is also consistent with the finding that reduced serotonergic function in patients with personality disorder is associated with high impulsivity [59]. Therefore, low 5-HT levels or dysfunction at the receptor level may underpin the symptomatic profile of impulse control disorders, possibly through a loss of executive control. However, this is based on very limited evidence from the results of the present study and should be considered tentatively, but may warrant examination in future research.

Furthermore, studies have demonstrated that impaired performance on 'executive-type' tasks in Parkinson's Disease can be overcome by some individuals through a shift to processing within the declarative memory system [55]. Conversely, in patients with frontal lobe damage who perform within normal limits on executive tasks, performance can be compromised if specific test instructions are given thereby 'switching' from a relatively automatic process to one more 'supervisory' in nature [56,57]. While the disruption of a single neurotransmitter system through ATD is not directly comparable to the structural damage described above, it may be possible that some subjects are

capable of altering strategy and maintain normal levels of performance.

Conclusions

In summary, the robust nature of the amino-acid tryptophan depletion paradigm has again been demonstrated. Significant depletion of plasma TRP levels was achieved, which had no effect on mood but speeded simple reaction times on a test of attention in line with the findings of many previous studies. Methodological problems limit our understanding of the role of 5-HT in executive functions. Larger studies may allow detailed analysis of the frequently observed interaction effects, or parallel group designs may be required which are not affected by carry-over effects or task familiarity, a significant confound when utilising tests of executive function which can be dependant upon novelty [58].

Competing Interests
None declared.

Authors' Contributions
R.H.McA.-W contributed to the design, supervision of the research, analysis of data and the writing up. P.G. contributed to the design, analysis of data and the writing up. A.E.M. contributed to the design, recruiting of subjects, the technical procedures and the writing up. A.H.Y. contributed to the design, analysis of data and the writing up.

Acknowledgements

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-244X/3/10/prepub