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# The effects of acute tryptophan depletion on neuropsychological function, mood and movement in the healthy elderly

Janet L Mace<sup>1</sup>, Richard J Porter<sup>2,3</sup>, John C Dalrymple-Alford<sup>3,4,5</sup>, Keith A Wesnes<sup>6</sup> and Tim J Anderson<sup>3,5</sup>

## Abstract

Few studies have investigated the function of the serotonin (5-HT) system in the elderly. Previous studies have shown effects of reducing serotonin function, by acute tryptophan depletion (ATD), on neuropsychological function in healthy subjects but this technique has not previously been employed over a wide age range in the elderly. This study compared the effects of ATD on mood, cognitive function and motor function in two groups of healthy volunteers, one group aged 50–69 and the other aged 70–89. The effects of ATD were investigated in a double-blind, placebo-controlled, counterbalanced, crossover, randomized design. The effects of ATD were not significantly different between age groups, suggesting that there is relatively little functional change across these age ranges. Compared with studies in much younger age groups there was, however, more evidence of an adverse effect of ATD on psychomotor function and working memory. There was no effect of ATD on mood despite inclusion of subjects with a family history of depression.

## Keywords

Mood, serotonin, tryptophan depletion

## Introduction

While there are informative post-mortem and imaging studies of the effects of aging on the serotonin (5-HT) system (Francis et al., 1993; Meltzer et al., 1998), there have been relatively few studies investigating the function of the 5-HT system in aging. One way of investigating serotonin function in humans is to study the effects of rapidly reducing brain serotonin using the technique of acute tryptophan depletion (ATD).

There is growing consensus from studies of the effects of ATD on cognitive function in younger subjects that 5-HT function has a role in encoding and consolidation (Riedel, 2004). It is possible that serotonin also modulates attention and frontally directed cognitions (Ahveninen et al., 2002; Booij et al., 2005; Gallagher et al., 2003; Riedel et al., 2002; Schmitt et al., 2000). Studies that have examined the effects of ATD in older adults have found broadly similar effects but have not been of sufficient size to examine its influence across different age ranges in the elderly (Mace et al., 2008; Porter et al., 2000, 2003, 2005; Scholtissen et al., 2006). One re-analysis of the data from these studies (Sambeth et al., 2007) did examine the effect of age on the effects of ATD in a single task of verbal memory and found that age did not modify the effects of ATD on verbal memory. However, other cognitive functions were not examined and the study included relatively few participants in the age range 70–90 years.

In previous studies in elderly subjects with neuropsychological disease, we have suggested that the combination of the serotonergic deficit induced by ATD interacts with cholinergic deficit to give rise to reduced cognitive function during ATD (Mace et al., 2009; Porter et al., 2003, 2005). There is some evidence of cholinergic change with aging in healthy subjects (Court et al., 1997), suggesting that the same interaction may be seen during ATD in the elderly.

The role of the 5-HT system in depression has also been investigated using the technique of ATD. Studies in younger

<sup>1</sup>School of Medicine and Pharmacology, University of Western Australia, Perth, Australia.

<sup>2</sup>Department of Psychological Medicine, University of Otago, Christchurch, New Zealand.

<sup>3</sup>Van der Veer Institute, Christchurch, New Zealand.

<sup>4</sup>Department of Psychology, University of Canterbury, Christchurch, New Zealand.

<sup>5</sup>Department of Medicine, University of Otago, Christchurch, New Zealand.

<sup>6</sup>United BioSource Corporation, Goring, UK.

## Corresponding author:

Richard J Porter, Department of Psychological Medicine, University of Otago, Christchurch, PO Box 4345, Christchurch, New Zealand  
Email: richard.porter@otago.ac.nz

subjects have shown that ATD may lower mood significantly in subjects who have recovered from depression (Booij et al., 2002) and in females with a family history of depression (Ellenbogen et al., 1999). In contrast, elderly subjects who had recovered from depression have shown no effect of ATD on mood (Porter et al., 2005), despite several participants having characteristics which appear to predispose to a mood-lowering effect of ATD (Booij et al., 2002). No previous study has systematically investigated the effects of ATD on mood in elderly subjects across a range of ages.

The serotonin system may also play a role in motor function, particularly in the elderly in whom use of serotonin re-uptake inhibitors, for instance, appears to pose increased risk of extrapyramidal side effects (Gormley et al., 1997) and falls (Hartikainen et al., 2007). This may occur through the interaction between the serotonin and dopamine systems, which may be exaggerated in elderly patients because of a relative reduction in dopamine activity (Volkow et al., 1998). In a previous study using ATD in healthy subjects and subjects with Parkinson's disease (PD), with a mean age of approximately 61 years, ATD reduced reaction times in a simple task of psychomotor speed across both groups (Scholtissen et al., 2006). This may be secondary to the removal of an inhibitory effect of serotonin on dopamine function.

The current study therefore sought to investigate the effects of ATD on cognitive function, mood and motor function in a group of healthy subjects across the age range 50–90, specifically to compare the effects of ATD in the younger (50–69) and older (70–90) age groups.

### Participants

Healthy older volunteers were recruited from local service clubs and a volunteer database at the Van der Veer Institute for Parkinson's and Brain Research in Christchurch, New Zealand. Exclusion criteria included a history of affective or other psychiatric disorder, serious medical disease, serotonergic medication, and a Mini-Mental State examination (MMSE, see below) score of  $\leq 26$ . The study comprised healthy adults aged over 50 years, recruited to give two groups based on age: younger (50–69 years) and older (70–89 years). All participants participated voluntarily and gave written informed consent. The study received ethical approval from the Upper South B Regional Ethics Committee, Christchurch, New Zealand.

### Design

The study used a double-blind, placebo-controlled, counter-balanced, crossover, randomized design. Every participant received both placebo and depleting (ATD) treatment in accordance with the study design, at least 1 week apart. The placebo comprised a drink of amino acids balanced to match human milk; ATD was the same mixture minus tryptophan (TRP). The composition of amino acids was as per Young et al. (1985) whisked with 250 g water. Males received 104.4 g of each treatment and females received 80% of this dose. The 83.3 g mixture given to females was based on the premise that females have a nearly 20% lower average weight (Ellenbogen et al., 1996).

## Measures

### Biochemical

Free plasma TRP was measured from venous blood samples which were placed on ice for approximately 15 min and ultra filtered. Samples were frozen at  $-80^{\circ}\text{C}$  until assay. The minimum measurement of TRP obtainable with the chromatography apparatus used in the present study was 500 ng/mL. All measurements below this level were classified as this minimum.

### Mood

Mood was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Profile of Mood States (POMS) (McNair et al., 1992). Two items (Reduced Appetite and Reduced Sleep) were removed from the MADRS (as per Booij et al., (2005)) because they would not change across the course of the testing. Two changes were made on the POMS during analysis in accordance with the manual instructions: all positive adjectives were deleted and the weighting on 'Relaxed' and 'Efficient' was reversed. The direction of POMS scoring now matched the MADRS, and at each observation a higher score indicates more mood symptoms.

### Movement

Movement was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) Section III Motor examination (Fahn et al., 1987). A higher score represents more disability.

### Neuropsychological

Cognitive tasks were administered in the following order: *Choice Reaction Time* (CRT) from Cognitive Drug Research (CDR) system (Simpson et al., 1991); *Motor Screening* (MOT), *Pattern Recognition Memory* (PRM), *Simultaneous and Delayed Matching to Sample* (SMTS, DMS), *Spatial Recognition Memory* (SRM), *Spatial Span* (SSP), *Spatial Working Memory* (SWM) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al., 1994); *Immediate Word Recognition* (IWR), *Delayed Word Recognition* (DWR), *Digit Vigilance* (DV) and *Simple Reaction Time* (SRT) from CDR; *Modified Mini-Mental State examination* (3MS) (Teng and Chui, 1987); *Digit Span* (Digit Span Forward, DigitsF; Digits Span Backwards, DigitsB) (Wechsler, 1981); *Digit Ordering Test* (DOT) (Werheid et al., 2002); *Incomplete letter and silhouettes* from the *Visual Object and Space Perception* test (VOSP) (Warrington and James, 1991); *Controlled Oral Word Association* test (COWA) (Benton and Hamsher, 1976).

### Procedure

After an overnight fast, healthy older volunteers attended the Van der Veer Institute in Christchurch. Treatment was administered at 9.00 am (baseline) and the drink consumed

within 15 min, after which participants rested until cognitive testing at 4.5 h. A 10 mL blood sample was taken at 0 h (baseline), 4 h and 6.5 h post treatment. The UPDRS and MADRS were administered at 0, 4.5, and 6.5 h. The CANTAB and CDR batteries were randomized to group and gender as per a crossover and counterbalanced design. On completion of testing, participants were given a light meal of mixed protein and carbohydrate to restore a healthy amino acid balance and to reverse any effects of the tryptophan depletion.

### Analysis

Data were analyzed using repeated measures analysis of variance (ANOVA). In the primary analysis ATD (depletion or placebo) was entered as a within-subject factor and group (younger or older), gender (given consistent findings of greater effects in females (Sambeth et al., 2007)) and order (placebo first or placebo second) as between-subject factors.

Order effects were investigated if there was a significant three-way interaction of treatment by group by order and, if not evident, then the ANOVA was re-run without order. In the analysis of mood, family history was added as a between-subject factor. For tryptophan, UPDRS and mood rating scales (the only ratings repeated at three time points during each test day), time was added as a within-subjects factor.

Significant treatment by group interactions were further explored by comparing ATD and placebo within each group using post hoc, paired samples *t*-tests.

## Results

In total, 43 subjects entered the study: younger (50–69 years;  $n = 21$ ) and older (70–90 years;  $n = 22$ ). There were no differences between groups on MADRS, MMSE, UPDRS, or pre-verbal IQ (PVIQ) (National Adult Reading Test, NART) (Nelson, 1982), measured at screening, as shown in Table 1. Both groups were taking non-serotonergic medications for cardiovascular (young: 1; old: 9) or other conditions (young: 13; old: 20) (full details available from authors on request).

Participant characteristics are presented in Table 1 and ANOVA results in Table 2. Where no significant effects of ATD or interactions between group and ATD were found the results are presented only in Table 2.

Data from 35 of the participants (mean age 69.2) have been presented previously in an analysis comparing the effects of ATD in healthy subjects compared with PD (Mace et al., 2010).

### Family history of depression

Of the 43 participants, 11 had a family history of depression. The grouping (male/female) for this was: younger (2/4); older (3/2).

### Missing data

Missing data included: Biochemical (1 younger and 1 older male/4 younger and 4 older females); POMS (1 younger and 1 older male/1 younger female); CRT Accuracy and Reaction Time (1 younger and 1 older male/1 younger female); SWM Between errors (1 older male).

### Treatment order

Twenty-one participants received the placebo drink first and ATD second (placebo/ATD) and 22 received the ATD drink first and placebo second (ATD/placebo); there were no significant three-way order effects.

### Biochemical

There was a significant interaction between treatment and time ( $F_{1,29} = 109.72$ ,  $p < 0.001$ ); during ATD this represented a 69% reduction in free TRP at 4 h and 69% at 6.5 h; during placebo a 173% increase in free TRP at 4 h and 69% at 6.5 h. There was a significant three-way interaction between treatment, time and group ( $F_{1,29} = 6.45$ ,  $p = 0.03$ ). During depletion, at 4 h and 6.5 h the younger group showed reductions of 64% and 62%, respectively, while for the older group the reductions were 70% and 71%. During placebo the younger group showed increases of 154% and 33% at these time

**Table 1.** Participant characteristics

	Younger			Older		
	M	SD	Range	M	SD	Range
Age	59.57	5.94	50–68	78.45	5.98	70–88
PVIQ	112.14	11.14	94–128	109.82	9.64	90–124
MMSE	29.52	0.98		29.23	1.02	27–30
MADRS	0.24	0.54	0–2	0.64	1.0	0–3
POMS	8.21	4.13	3–18	10.48	8.75	0–32
UPDRS	0.55	1.15	0–5	2.09	2.41	0–7
<i>n</i> (m/f)	21 (10/11)			22 (12/10)		

M: mean, SD: standard deviation, *n*: number, m: male, f: female, PVIQ: predicted verbal IQ, MMSE: Mini Mental State examination, MADRS: Montgomery–Asberg Depression Rating Scale, POMS: Profile of Mood States, UPDRS: Unified Parkinson's Disease Rating Scale.

**Table 2.** Effects of treatment (ATD versus placebo) on all variables. Repeated measures ANOVA

Variable	Younger (50-69 years)				Older (70-89 years)				Treatment × Age Group × Gender			
	ATD		Placebo		ATD		Placebo		Treatment		×	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	df	F Sig	F Sig	F Sig
3MS Total	99.71	2.17	98.52	2.32	96.77	3.82	96.14	5.06	1,39	3.53	0.22	0.22
MMSE Total	29.67	0.91	29.52	0.75	29.23	1.23	29.68	2.17	1,39	0.34	1.27	0.86
DigitsF Total	9.86	2.17	9.48	2.34	8.91	2.37	9.00	2.37	1,39	0.39	1.05	1.93
DigitsB Total	7.95	2.73	7.43	3.17	6.55	1.68	6.50	2.24	1,39	1.14	0.80	2.32
DOT Total	7.90	2.81	7.43	1.94	7.50	2.74	7.14	2.55	1,39	1.33	0.06	1.08
COWA Total	47.43	17.611	48.43	14.218	37.95	11.524	39.18	10.720	1,39	0.68	0.00	0.01
SSP Span	5.05	1.24	5.48	1.12	4.73	0.98	5.05	0.84	1,39	<b>7.82**</b>	0.13	0.13
SWM Between Errors	36.86	20.65	37.38	16.49	46.76	20.42	40.38	14.74	1,38	1.20	1.56	0.68
IWR SI	0.90	0.13	0.90	0.12	0.87	0.12	0.83	0.13	1,39	0.83	1.34	1.12
DWR SI	0.83	0.14	0.88	0.14	0.77	0.21	0.78	0.14	1,39	1.17	0.18	1.81
VOSP Incomplete Letters	19.57	0.60	19.38	0.92	19.45	0.74	19.50	0.60	1,39	0.32	1.03	2.85
VOSP Silhouettes	11.00	2.30	9.57	3.11	9.32	1.94	10.00	2.49	1,39	0.56	3.77	0.38
PRM Accuracy	88.33	10.70	91.04	8.79	85.80	11.11	90.34	4.88	1,38	3.94	0.20	0.14
PRM Reaction time	2099.30	456.01	2079.85	506.95	2384.53	438.97	2361.02	434.17	1,38	0.19	0.01	0.37
SRM Accuracy	73.81	12.44	78.81	14.48	74.32	11.58	76.14	10.68	1,39	2.15	0.37	0.08
SRM Reaction time	2147.13	524.69	2224.01	478.62	2525.82	744.82	2306.94	704.86	1,39	0.83*	<b>4.50*</b>	3.90
SMTS Accuracy	97.14	97.147	98.10	8.73	92.27	13.07	93.64	9.02	1,39	0.29	0.01	0.11
SMTS Reaction time	3213.00	1130.96	3171.52	643.04	3364.38	1011.26	3746.13	1209.22	1,39	1.50	2.02	0.41
DMS Accuracy	82.70	14.74	86.35	8.56	77.73	13.85	84.85	10.48	1,39	<b>5.03*</b>	0.36	3.94
DMS Reaction time	4022.64	1275.31	3923.12	1070.19	4226.00	1489.02	4222.73	1476.99	1,39	0.02	0.14	0.86
DMS %Corr	86.31	11.34	89.29	6.76	81.36	11.54	87.05	8.78	1,39	<b>5.58*</b>	0.37	<b>4.19*</b>
MOT Accuracy	8.74	1.97	8.89	2.51	10.29	3.27	10.59	2.84	1,39	0.18	0.02	0.01
MOT Reaction time	1208.56	224.14	1122.00	282.21	1405.61	394.33	1324.39	367.40	1,39	<b>5.15*</b>	0.01	0.06
CRT Accuracy	290.53	8.15	290.53	9.70	289.50	9.45	289.25	6.93	1,35	0.01	0.01	0.09
CRT Reaction time	1360.48	153.99	1353.53	133.25	1480.34	152.95	1435.36	144.97	<b>1,36</b>	<b>5.16*</b>	2.78	0.06
SRT Reaction time	293.00	39.29	303.46	46.05	355.51	59.85	342.01	57.28	1,39	0.04	2.40	0.00
DV Accuracy	100.0000	.00000	98.73	3.412	98.1823	4.68216	99.39	2.842	1,39	0.01	2.63	1.35
DV Reaction time	421.0252	51.69582	430.3400	45.00372	436.7909	33.73145	434.6345	31.44763	1,39	1.43	1.70	0.78

\* $p \leq 0.05$ , \*\*  $p \leq 0.01$ .

Note: COWA: Controlled Oral Word Association test, CRT: Choice Reaction Time, DigitsB: Digit Span Backward, DigitsF: Digit Span Forward, DMS: Delayed Matching to Sample, DWR: Delayed Word Recognition, DOT: Digit Ordering Test, DV: Digit Vigilance, IWR: Immediate Word Recognition, MMSE: Mini Mental State examination, 3MS: Modified Mini Mental State examination, MOT: Motor Screening, SMTS: Simultaneous Matching to Sample, SRM: Spatial Recognition Memory, SRT: Simple Reaction Time, SSP: Spatial Span, SWM: Spatial Working Memory, VOSP: Visual Object and Space Perception test.

points, while for the older group the increases were 194% and 108%.

### Mood

There was no significant interaction between treatment and time on MADRS ( $F_{2,39} = 0.14$ ,  $p = 0.88$ ) or POMS ( $F_{2,36} = 0.71$ ,  $p = 0.49$ ) and no three-way interaction between treatment, group and time for either MADRS ( $F_{2,39} = 0.11$ ,  $p = 0.90$ ) or POMS ( $F_{2,39} = 0.63$ ,  $p = 0.53$ ). When family history (positive versus negative) was added to the analysis, there was no interaction between treatment, family history and time for either MADRS or POMS.

### Movement

There was no significant interaction between treatment and time on UPDRS ( $F_{2,39} = 0.45$ ,  $p = 0.64$ ) and no three-way

interaction between treatment, group and time ( $F_{2,39} = 0.22$ ,  $p = 0.81$ ).

### Psychomotor speed

There was a significant main effect of treatment on CRT Reaction Time ( $F_{1,36} = 5.16$ ,  $p = 0.029$ ). Participants were slower during ATD ( $M = 1419.86$ ,  $SD = 162.68$ ) compared with placebo ( $M = 1397.09$ ,  $SD = 142.17$ ). There was also a significant main effect of treatment on MOT Reaction Time ( $F_{1,40} = 5.15$ ,  $p = 0.029$ ). Participants were slower during ATD ( $M = 1309.37$ ,  $SD = 334.07$ ) compared with placebo ( $M = 1225.55$ ,  $SD = 340.44$ ). There was a significant interaction between treatment and age group on SRM Reaction Time ( $F_{1,39} = 4.50$ ,  $p = 0.04$ ). The reaction time of the older group was significantly longer during ATD ( $M = 2525.82$ ,  $SD = 744.82$ ,  $F_{1,21} = 2.27$ ,  $p = 0.033$ ) compared with placebo ( $M = 2306.94$ ,  $SD = 704.86$ ), while the younger group were only marginally



faster during ATD ( $M = 2147.13$ ,  $SD = 524.69$ ) compared with placebo ( $M = 2224.01$ ,  $SD = 478.62$ ).

### Memory

There was a significant main effect of treatment on DMS Accuracy ( $F_{1,39} = 5.03$ ,  $p = 0.03$ ). Participants were less accurate, making more errors during ATD ( $M = 80.15$ ,  $SD = 14.35$ ) compared with placebo ( $M = 85.58$ ,  $SD = 9.50$ ).

There was also a significant main effect of treatment on the closely related variable DMS %Correct ( $F_{1,39} = 5.58$ ,  $p = 0.023$ ). Participants were less accurate during ATD ( $M = 83.78$ ,  $SD = 11.58$ ) compared with placebo ( $M = 88.14$ ,  $SD = 7.85$ ).

There was also a significant interaction between treatment and gender on DMS %Corr ( $F_{1,39} = 4.19$ ,  $p = 0.047$ ). Male performance was worse during ATD ( $M = 76.36$ ,  $SD = 13.6$ ) compared with placebo ( $M = 86.3$ ,  $SD = 10.8$ ), while there was little difference in the performance of females during ATD ( $M = 84.1$ ,  $SD = 2.1$ ) compared with placebo ( $M = 84.8$ ,  $SD = 8.1$ ).

### Working memory

There was a main effect of treatment on Spatial Span ( $F_{1,39} = 7.82$ ,  $p = 0.008$ ). Participants performed more poorly during ATD ( $M = 4.9$ ,  $SD = 1.1$ ) compared with placebo ( $M = 5.3$ ,  $SD = 1.0$ ).

## Discussion

The present study is the first ATD study to examine the influence of age and gender specifically in healthy older persons. The principal findings were as follows:

There was no effect of ATD on mood and no specific effect in those with a history of depression in a first-degree relative. ATD was associated with slower performance on two separate tasks assessing psychomotor speed, and in a further task the older group performed more slowly during ATD. ATD was associated with poorer visual memory performance.

ATD was associated with poorer visual working memory performance.

Regarding mood, previous studies in healthy subjects have shown little effect of ATD except when subjects have had a family history of depression or mood disorder (Benkelfat et al., 1994; Klaassen et al., 1999; Sobczak et al., 2002). The effect in subjects with a family history is not absolutely consistent (Ellenbogen et al., 1999), but is supported by a meta-analysis (Ruhe et al., 2007). In the current study, 12 of 43 participants had a history of major depression in a first-degree relative. However, there was no effect of mood specific to these participants measured either on the MADRS or POMS. There are at least two possible reasons for this finding, which contrasts with the data in younger age groups (Ruhe et al., 2007). First, the group with a positive family history was relatively small and therefore the analysis may

have lacked power to detect a significant effect in this subgroup. Second, the lack of an effect on mood in this group could imply that the elderly are less susceptible to mood effects of a rapid reduction in brain serotonin. Support for this explanation comes from the finding that, despite a high incidence of established risk factors (Booij et al., 2002), a group of elderly subjects recovered from depression also showed no mood response to ATD (Porter et al., 2005). Clinically, it could be suggested that the data may imply that serotonergic drugs may be less likely to be effective in depression in the elderly. However, there is little evidence that this is the case (Roose and Schatzberg, 2005).

Our previous report (Mace et al., 2010) examined the effects of ATD on mood in PD and healthy controls and included data from a number of the healthy controls in the current study. There was a significant but very small effect of ATD on MADRS, with a worsening at 6.5 h compared with placebo. However, there was no group by ATD interaction, so data on the controls were not analyzed separately. The current analysis in a larger number of healthy controls suggests that there is no effect on mood in this expanded and entirely healthy group. This is also in keeping with our other previous studies in the healthy elderly (Porter et al., 2003, 2005).

We have previously reported an increase in latency of response on the motor screening task in healthy elderly controls during ATD (Mace et al., 2009). The current study represents an expansion of the control group in that report, both in terms of numbers and an older mean age. The increase in latency during ATD in the motor screening task in the current study, is consistent with the previous report (Mace et al., 2009) and is supported by the finding in this analysis of an increase in latency on the Choice Reaction Time Test during ATD, suggesting more strongly that this is a genuine effect and not a chance finding. In addition, there was a similar increase in reaction time during ATD on the spatial recognition task, specific to the older age group. The effects of ATD on psychomotor speed in this study and our previous study (Mace et al., 2009) are in contrast to a previous report (Scholtissen et al., 2006) which found reduced reaction times during ATD across both healthy and PD groups. However, in the study of Scholtissen et al. the control group was small ( $n = 15$ ) and younger (mean age 61 years). In two other studies there was no significant effect of ATD on psychomotor measures in healthy elderly controls (Porter et al., 2003, 2005). These groups had a similar mean age to the current study but both were considerably smaller groups ( $n = 16$  and  $n = 17$ ), and in one of the studies a smaller (50 g) drink was used. In both previous reports in PD (Mace et al., 2009; Scholtissen et al., 2006), ATD improved psychomotor speed on a number of measures in the patients with PD. The current study therefore suggests a reduction in psychomotor speed in older healthy subjects during ATD which may not have been apparent in previous studies because of a younger age and smaller groups. In PD, in contrast, removal of the inhibitory effect of serotonin on dopamine may result in an increase in dopamine function and increased psychomotor speed. In the elderly compared with younger subjects, serotonin may have a more direct role in maintaining psychomotor function and its lowering may therefore have a detrimental effect.

The older group, as expected, were taking more medication, primarily beta-blockers, diuretics and ACE inhibitors for hypertension and statins. While it is possible that these may have cognitive effects and affect psychomotor speed, it is less likely that they would mediate a differential effect of ATD.

This study, in common with most others investigating the effects of ATD on neuropsychological function, employed a number of tasks which generated a number of outcome variables, giving rise to the likelihood of chance findings. The significant reduction in scores on the closely related variables Delayed Matching to Sample accuracy and percentage correct during ATD, with a greater effect on percentage correct in males, may well be a chance finding since it does not fit well into the wider pattern of change.

In the present study, spatial span was significantly reduced during ATD. Once again this does not appear to fit into a wider pattern and may be a chance finding. However, several studies in older groups have shown statistically significant effects on aspects of working memory, including on the analogous digit span task (Kilkens et al., 2004; Mace et al., 2008; Porter et al., 2003, 2005). Studies investigating the effects of age on the spatial span task show that performance declines with age (Robbins et al., 1998). It may be that the apparent greater effect of ATD on various tasks measuring working memory in older subjects is a function of the tasks being more difficult, and therefore more sensitive, in this age group.

The percentage reduction of tryptophan after ATD is in line with the level of reduction found in ATD studies with older participant groups (Leentjens et al., 2006; Porter et al., 2000, 2005). It should be noted, also, that the lowest level the assay used in this study could detect was 500 ng/mL, which may have artificially elevated the depletion level. A limitation of the study, however, is that we were unable to measure tryptophan/large neutral amino acid (TRP/LNAA) ratio, which would have given a more accurate estimate of TRP availability to the brain than free TRP levels. This would have confirmed a reduction in central TRP availability during the depletion arm of the study and indicated whether the placebo arm was likely to be neutral in regard to TRP/LNAA ratio. However, previous studies have confirmed that similar manipulations in other patient groups (but not the elderly) have reduced TRP/LNAA ratio by 70–90% and resulted in no change following placebo (Golightly et al., 2001). There was a significant difference in TRP levels over time between the two groups. The greatest difference was in the placebo TRP levels, which were considerably more elevated and did not decline as rapidly in the older group. This may be explained by less efficient catabolism of the TRP load by the liver. Reduction in TRP was significantly less in the younger group, surprisingly, if indeed catabolism is slower in the older group. A possible explanation is that the protein load reduces insulin secretion and that the elderly are relatively less sensitive to the resulting low insulin levels. Since insulin favors entry of LNAA's rather than TRP into the tissues, levels would be higher in the younger subjects. The difference is unlikely to have had an effect on results since there was only one group-specific result.

## Conclusion

This is the largest study to investigate the effects of ATD in healthy elderly and has studied the oldest group in which this technique has been used. The technique was tolerable and large reductions in peripheral TRP were seen. Despite this, ATD induced only subtle changes in cognitive function which were not dependant on age group, suggesting that even in the oldest subjects there was sufficient reserve of serotonin function or that other systems are able to compensate, in order to maintain most functions during ATD. Compared with younger groups, the elderly may be more susceptible to an adverse effect of ATD on psychomotor function and working memory.

The finding of a lack of effect on mood even in those with a family history is intriguing, particularly when added to our previous finding of a lack of an effect in elderly subjects recovered from depression (Porter et al., 2005), and may suggest a reduced influence of low serotonin function on mood in the elderly.

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## Conflict of interest statement

The authors have no conflicts of interest to declare.

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