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Effects of acute tryptophan depletion on neuropsychological and motor function in Parkinson's disease

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Abstract

Interactions between the 5-HT system and the dopaminergic system and cholinergic system may be important in determining cognitive function and motor function in Parkinson's disease (PD). Previous studies have shown effects of reducing serotonin function, by acute tryptophan depletion (ATD), on neuropsychological function. In particular, an adverse effect on verbal memory has been demonstrated. This study compared with the effects of ATD on cognitive and motor function in PD and healthy control subjects. The effects of ATD were investigated in a double-blind, placebo-controlled, counterbalanced, cross-over, randomised design in 20 patients with PD and 35 healthy controls matched for age, gender and premorbid IQ. There was a differential group effect of ATD on global cognitive function whereby the mean score on the modified mini mental state examination during ATD was lower than placebo in PD but higher in controls. There was a similar pattern of effects on verbal recognition. In a visual recognition task, ATD improved performance in the PD but not in the control group. In terms of psychomotor speed, there was also a group-specific effect with reduced latency of response during ATD in the PD group but increased latency in the control group. ATD has subtle neuropsychological effects, which differ significantly between PD and healthy control subjects. This suggests that the dopaminergic and cholinergic deficit of PD significantly modulates the effects of serotonin depletion, resulting in positive effects in some domains. Further investigation on the effects of specific serotonin antagonists may be merited in PD.

Key words

acute tryptophan depletion; cognition; memory; motor symptoms; movement; Parkinson's disease; serotonin

Introduction

The efficacy of current medication for cognitive impairment in Parkinson's disease (PD) is relatively limited. Cholinesterase inhibitors are most widely used in senile dementia of the Alzheimer's type (SDAT) but more evidence is required regarding their efficacy in PD (for a review of studies see, Aarsland, *et al*., 2004). Considerable animal research suggests that the serotonin (5-HT) system may provide an additional approach to cognitive remediation, and there are efforts to develop cognitive enhancers acting on the 5-HT system, in particular 5-HT_{1A} antagonists, which have been shown to alleviate learning impairment in animal models of dementia (Harder, *et al*., 1996a; Schechter, *et al*., 2002). Evidence also suggests a role of 5-HT in some of the motor symptoms in PD, in addition to the loss of dopamine (DA) projections from the substantia nigra pars compacta to the striatum (Dauer and Przedborski, 2003). For example, there is evidence of a correlation between 5-HT_{1A} binding in the raphe and tremor (Doder, *et al*., 2003), and extrapyramidal symptoms are increased in some PD patients treated with selective serotonin reuptake inhibitors (SSRIs) (Schillevoort, *et al*., 2002).

It is also possible that interactions between the 5-HT system and the dopaminergic system and/or the cholinergic system may be important in determining cognitive function in PD.

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Neuroimaging and pharmacological data suggest links between dopaminergic and cholinergic system integrity and neuropsychological performance, for example, in tasks of executive function and working memory (Rinne, *et al*., 2000). Degeneration in the cholinergic system may be particularly important (Bohnen, *et al*., 2006), because it is more severely affected in PD than in Alzheimer's disease (SDAT) (Bohnen, *et al*., 2003).

Dietary restriction of tryptophan amino acid has become a standard procedure to examine the effects of acute reduction in brain 5-HT (Reilly, *et al*., 1997) and this approach has provided some support for an interaction between cholinergic and serotonergic systems in SDAT (Porter, *et al*., 2000). A reduction in global cognitive status in SDAT patients was found after acute tryptophan depletion (ATD) but there was also an improvement in pattern recognition, at least in woman with SDAT (Porter, *et al*., 2003). The only study of ATD in PD thus far reported examined the effects of ATD on executive function and memory specifically and showed no effects specific to the PD group compared with matched healthy controls. However, there was no clinical measure of global cognitive status (Scholtissen, *et al*., 2006).

The current study revisited the effects of reduced 5-HT level on cognitive function and motor function in PD in a larger sample of patients. Given the effects of ATD in SDAT, we hypothesised that a reduction in central 5-HT levels may worsen global cognitive status as measured by the modified mini-mental state examination (3MS) (Teng and Chui, 1987) but would produce beneficial effects on pattern recognition. In addition, a broader range of neuropsychological measures than used previously (Scholtissen, *et al*., 2006) was used in this study to address the range of cognitive impairments that can be found in PD patients.

Patients and methods

Participants

PD patients, as defined by the UK Parkinson's Society Brain Bank criteria (Hughes, *et al*., 1992), had received specific neurological and physical examinations by movement specialist neurologists within the past year. Exclusion criteria includes the history of affective or other psychiatric disorder, serious medical disease, serotonergic medication and a mini-mental state examination (MMSE) (Folstein, *et al*., 1975) score of <27. Controls were excluded as per patient criteria plus an absence of PD. 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 had a double-blind, placebo-controlled, randomised, counterbalanced, cross-over design. Every participant received both placebo and 5-HT depleting (ATD) treatment at least 1 week apart (range = 1–2 weeks). The placebo comprised a drink with amino acids balanced to match human milk; ATD was the same mixture without tryptophan (TRP). The composition of amino acids was, as per Young, *et al*., (1985), whisked with 250 g water. Men received 104.4 g for each treatment and woman received 80% of this dose, based on the premise that females have a nearly 20% lower average weight (Ellenbogen, *et al*., 1996).

Measures

Biochemical Free plasma tryptophan was measured from venous blood samples, which were placed on ice for approximately 15 min and ultra-filtered. Samples were frozen until assay. The minimum measurement of tryptophan obtainable with the chromatography apparatus used in the current study was 500 ng/mL. All measurements below this level were classified as this minimum, and thus reductions in tryptophan levels may be lower than reported.

Movement Unified Parkinson's Disease Rating Scale (UPDRS) Section III. Motor examination (Fahn and Elton, 1987).

Neuropsychological testing

Cognitive tasks were administered in the following order: Choice Reaction Time (CRT) from Cognitive Drug Research (CDR) battery (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); Delayed Word Recognition (DWR), Digit Vigilance (DV), Immediate Word Recognition (IWR), Simple Reaction Time (SRT) from CDR; MMSE; Modified Mental State (3MS) examination (Teng and Chui, 1987); Digit Span (Digit Span Forward, DigitsF; Digits Span Backwards, DigitsB) (Weschler, 1981); Digit Ordering Test (DOT) (Werheid, *et al*., 2002); 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, participants presented to the Van der Veer Institute for PD and Movement Disorders in Christchurch (New Zealand) at 8:30 a.m. To allow absorption of levodopa to the brain before treatment and to maintain motor function during the test day, patients took their usual medication at 7:00 a.m. on the days of testing. If prescribed, participants took additional antiparkinsonian medication during the test day. Treatment was administered at 9:00 a.m. (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 baseline (0), 4 and 6.5 h post treatment. The UPDRS was administered at 0, 4.5 and 6.5 h. 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

SPSS for Windows Release 13 (SPSS, Chicago, Illinois, USA) was used for the statistical analysis. Data were analysed using repeated measures analysis of variance (ANOVA). In the primary analysis, treatment (ATD or placebo) was entered as a within subject factor and group (PD or control), gender and order (placebo first or placebo second) as between subject factors. When a task had delays or levels of difficulty then these variables were entered as an additional within subjects factor. Significant treatment by group interactions were further explored by comparing ATD and placebo within each group using Fisher's adjusted least significant difference (LSD) tests. Based on previous studies in older patient groups (Porter, *et al*., 2000, 2005), the primary outcome of this research was score on 3MS, which was reduced by 5 points during ATD in the SDAT group. The study was powered to have 80% power to show a mean difference of 5 points ($SD_{diff} = 5$) in a PD group when $n = 16$, at a two-tailed significance level of 0.05.

Results

Missing data

Biochemical data are missing for three patients and four controls; SWM data for two controls, and CRT accuracy and reaction time data for one patient and one control.

Demographic

Patients and controls were matched for gender, age and predicted IQ (PVIQ) from the National Adult Reading Test (Nelson, 1982). There was no significant difference between groups on these variables (Table 1).

Medication status

Nineteen of 20 patients were on parkinsonian medication as follows: levodopa-decarboxylase inhibitor ($n = 16$), peripheral DA antagonist ($n = 4$), DA agonist ($n = 14$), DA agonistanticholinergic ($n = 7$), anticholinergic ($n = 4$) and MAO-B inhibitor ($n = 5$).

Treatment order/gender

Twenty six participants received the placebo drink first and ATD second (placebo/ATD), and 29 received the ATD drink first and placebo second (ATD/placebo); there were no significant 3-way interactions between treatment, group and order or between treatment, group and gender.

Biochemical

At baseline, there was no significant difference in free TRP levels between the ATD ($M = 1765.97$, SD = 142.62) and placebo days ($M = 1850.00$, $SD = 124.09$; $t_{48} = 0.86$, $P = 0.39$); nor there was a significant difference between patients ($M = 1989.47$, $SD = 858.23$) and controls ($M = 1787.10$, $SD = 819.65$; $t_{48} = 0.83$, $P = 0.41$) on the ATD test day. As expected, free TRP levels were markedly reduced by ATD ($F_{1,42} = 178.23$, $P < 0.001$; free TRP during ATD, $M = 951.79$, SE = 44.29; free TRP during placebo, $M = 3509.23$, SE = 219.62.) There was a significant interaction of treatment and time ($F_{1,42} = 49.49$, $P < 0.001$), such that free

Table 1 Participant characteristics

	PD			Controls		
	Mean	SD	Range	Mean	SD	Range
Age (years)	67.8	5.72	59–84	69.23	11.61	50–88
PVIQ	106.5	8.81	84–118	108.11	9.27	90–123
MMSE	29.1	0.85	27–30	29.26	1.07	27–30
MADRS	1.75	2.02	0–4	0.4	0.85	0–3[a]
H & Y	2.18	0.78	1–4			
Age onset (years)	61.5	9.28	39–82			
Time from diagnosis (years)	6.75	6.23	0–25			
Side onset (*n*)	Left (5)	Right (14)	Unsure (1)			
n	20			35		
Gender (m/f)	12/8			21/14		

PVIQ, predicted verbal IQ score (from the NART: national adult reading test); MMSE, mini mental state examination; MADRS, Montgomery-Asberg depression rating scale; H & Y, Hoehn and Yahr score; f, female; m, male.

All comparisons are independent samples *t*-test except [a]Significance (Mann–Whitney test).

TRP was reduced from baseline by 71% at 4 and 6.5 h after ATD but increased by 177% at 4 h and 72% at 6.5 h after placebo, but this effect was similar in both groups.

Movement

There were no effects of treatment on the UPDRS and no treatment by group interaction.

Neuropsychological

Results for all variables are shown in Table 2. Only statistically significant results for individual assessments are presented and referred to in this text.

Modified mini-mental state examination

There was a significant interaction between treatment and group on 3MS ($F_{1,53} = 8.03$, $P < 0.007$). Patient performance was worse during ATD ($M = 94.70$, SE = 1.10) compared with placebo ($M = 97.15$, SE = 0.87), whereas control performance was enhanced during ATD ($M = 97.91$, SE = 0.83) compared with placebo ($M = 96.74$, SE = 0.66) (Figure 1A). Post hoc analysis showed no significant difference between ATD and placebo for both patients ($t_{19} = 1.90$, $P = 0.07$) and controls ($t_{34} = -1.87$, $P = 0.07$).

Immediate word recognition

There was a significant interaction between treatment and group on IWR ($F_{1,53} = 5.11$, $P = 0.03$). The performance of patients was worse during ATD ($M = 0.75$, SE = 0.04) compared with placebo ($M = 0.82$, SE = 0.03), whereas the performance of controls during ATD ($M = 0.87$, SE = 0.03) was marginally better compared with placebo ($M = 0.85$, SE = 0.03) (Figure 1B). Post hoc analysis showed no significant difference between ATD and placebo for either patients ($t_{19} = 1.79$, $P = 0.09$) nor the controls ($t_{34} = -1.12$, $P = 0.27$).

Simultaneous and delayed matching to sample

There was a significant interaction between treatment and group on DMS accuracy ($F_{1,53} = 7.06$, $P = 0.01$). The percentage correct scored by patients was enhanced during ATD ($M = 80.67$, SE = 3.12) compared with placebo ($M = 77.00$, SE = 2.39), whereas the performance of controls was worse during ATD ($M = 78.38$, SE = 2.36) compared with placebo ($M = 85.91$, SE = 1.80), as shown in Figure 1D. Post hoc analysis, however, showed no significant difference between ATD and placebo for either patients ($t_{19} = 1.79$, $P = 0.09$) or the controls ($t_{34} = -1.12$, $P = 0.27$). There was also a significant interaction between treatment and group on DMS % Correct ($F_{1,53} = 7.73$, $P = 0.008$). DMS % Correct is a different variable to DMS accuracy, in that it reports the percentage of times a correct response is made on a participant's first response rather than merely the percent correct responses in total, as occurs in DMS accuracy. The performance of patients was enhanced during ATD ($M = 84.50$, SE = 2.42) compared with placebo ($M = 81.25$, SE = 2.00), whereas the performance of controls was worse during ATD ($M = 82.43$, SE = 1.83) compared with placebo ($M = 88.29$, SE = 1.52). Post hoc analysis showed

Table 2 Effects of treatment (ATD vs. placebo) on movement and neuropsychological variables

	Variable	df	Treatment *F*	Treatment × Group *F*
UPDRS	Total	1,53	0.13	0.77
3MS	Total	1,53	1.00	8.03**
MMSE	Total	1,53	2.84	0.57
DigitsF	Total	1,53	0.40	0.04
DigitsB	Total	1,53	0.50	0.02
DOT	Total	1,53	1.13	1.54
COWA	Total	1,53	0.04	0.67
COWA	Violation errors	1,53	1.01	1.48
COWA	Repetition errors	1,53	0	0.75
VOSP	Incomplete letters	1,53	0.49	0.88
VOSP	Silhouettes	1,53	0.29	1.53
MOT	Accuracy	1,53	1.62	2.77
MOT	Reaction time	1,53	1.99	16.52***
PRM	Accuracy	1,53	1.57	0.98
PRM	Reaction time	1,53	0.01	0.25
SRM	Accuracy	1,53	0.01	1.01
SRM	Reaction time	1,53	0.03	0.33
SMTS	Accuracy	1,53	0.11	0.67
SMTS	Reaction time	1,53	3.69	0.91
DMS	Accuracy	1,53	0.84	7.06**
DMS	Reaction time	1,53	0.25	0.44
DMS	% Correct	1,53	0.63	7.73**
SSP	Span	1,53	3.82	0.48
SWM	Between errors	1,51	4.16*	0.61
CRT	Accuracy	1,49	0.33	0.84
CRT	Reaction time	1,49	0.02	3.98
SRT	Reaction time	1,53	1.66	1.11
IWR	Sensitivity index	1,53	1.1	5.11*
DWR	Sensitivity index	1,53	1.85	0.52
DV	Accuracy	1,53	0.04	0.14
DV	Reaction time	1,53	2.08	2.89

UPDRS, United parkinson's disease Rating Scale; 3MS, modified mini-mental state examination; MMSE, mini mental state examination; DigitsF, digit span forwards; DigitsB, digit span backwards; DOT, digit ordering test; COWA, controlled oral word association test; VOSP, visual object and space perception test; MOT, motor screening; PRM, pattern recognition memory; SRM, spatial recognition memory; SMTS, simultaneous matching to sample; DMS, delayed matching to sample; SSP, spatial span; SWM, spatial working memory; CRT, choice reaction time; SRT, simple reaction time; IWR, immediate word recognition; DWR, delayed word recognition; DV, digit vigilance.
*$P < 0.05$; **$P \leq 0.01$; ***$P < 0.001$.
Repeated measures analysis of variance (ANOVA).

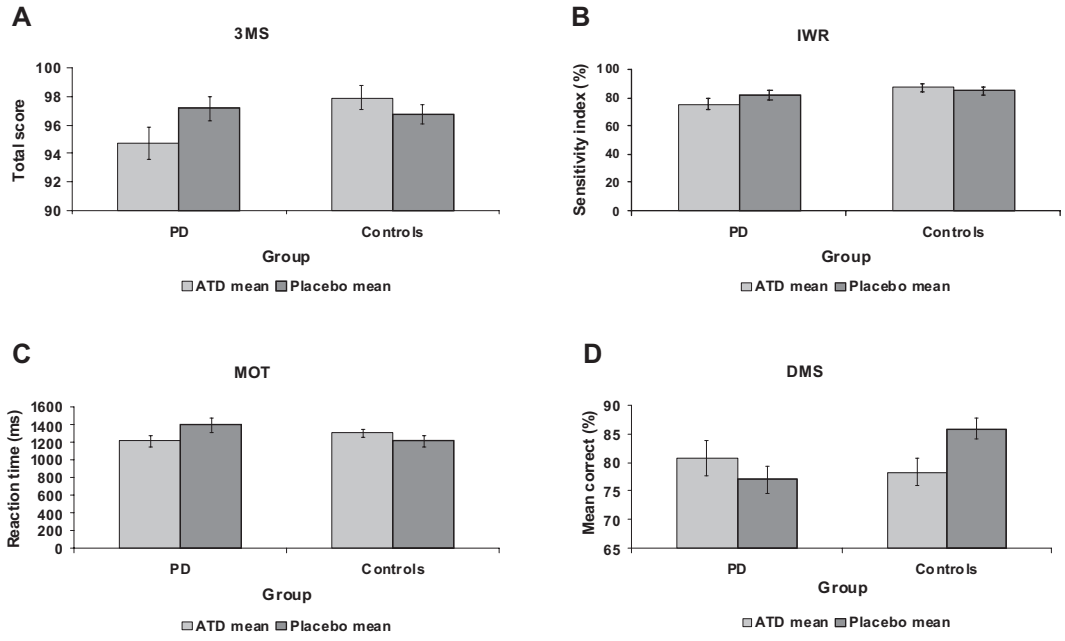

Figure 1 Effect of treatment and group on the modified mini-mental state examination (3MS), immediate word recognition (IWR), motor screening (MOT), delayed matching to sample (DMS). Note: A higher score reflects better performance, except for MOT where a lower score reflects better performance.

that the difference between ATD and placebo was significant for controls ($t_{34} = 2.94$, $P = 0.01$), but not for patients ($t_{19} = -1.15$, $P = 0.26$).

Spatial working memory

There was a significant main effect of treatment on SWM ($F_{1,51} = 4.16$, $P = 0.04$). The number of between search errors was greater during ATD ($M = 44.46$, SE = 2.73) compared with during placebo ($M = 40.25$, SE = 2.16).

Motor screening

There was a significant interaction between treatment and group on MOT ($F_{1,53} = 16.52$, $P < 0.001$) (Figure 1C). Patient response time was faster during ATD ($M = 1215.68$, SE = 70.85) compared with placebo ($M = 1403.80$, SE = 79.57), but control response time was slower during ATD ($M = 1303.51$, SE = 53.56) compared with placebo ($M = 1212.26$, SE = 60.15). Post-hoc analysis showed a significant difference between ATD and placebo for both patients ($t_{19} = 3.22$, $P < 0.01$) and controls ($t_{34} = -2.29$, $P = 0.03$).

Discussion

The present study investigated the effects of ATD on movement and cognition in 20 patients with PD and 35 healthy, age and gender matched controls. We have previously reported that in the same study ATD produced a statistically significant but small reduction in mood measured by a modified Montgomery-Asberg Depression Rating Scale score in both groups (Mace, *et al*., in press). There was also a significant reduction in free TRP during ATD in both groups.

The principal findings in the domains of cognition and movement are as follows (see also Figure 1).

1) There was a differential effect of ATD on global cognitive function whereby scores on the 3MS during ATD compared with placebo tended to decline in PD but increase in controls. There was a similar pattern of effects on verbal recognition.
2) In contrast, delayed visual matching to sample decreased significantly during ATD in the control group but tended to increase in the PD group.
3) In terms of psychomotor speed, there was a significant interaction between ATD and group with reduced latency of response during ATD in the PD group but increased latency in the control group.

Several previous studies have investigated the effects of ATD on cognitive function in healthy younger subjects. The most consistent finding has been that ATD reduces delayed verbal recall with fewer studies demonstrating reduced delayed visual recall during ATD (Riedel, 2004). In a mega-analysis of a mixed older and younger group, including participants with

various conditions thought to involve 5H-T vulnerability, ATD impaired delayed verbal recall and encoding of verbal material (Sambeth, *et al*., 2007).

In more directly comparable studies, involving older subjects, the effect of ATD on global cognitive function has been investigated in SDAT (Porter, *et al*., 2000, 2003). Porter, *et al*. (2000) found that ATD reduced 3MS score in SDAT but not in the healthy control group. It was hypothesised that this effect was secondary to the increased importance of 5-HT function in the presence of cholinergic deficit. Given the likely greater cholinergic deficit in PD (Bohnen, *et al*., 2003; Tiraboschi, *et al*., 2000), we hypothesised that the similar effect would be seen in PD and, in fact, this was the case. This was despite the fact that in the current study the PD patients were not globally cognitively impaired at baseline, and therefore likely to be operating at a point close to ceiling level on this task. As noted earlier, another comparable study in PD (Scholtissen, *et al*., 2006) did not include an assessment of global cognitive status and cannot, therefore, be compared in this regard.

Interestingly, a similar pattern on the 3MS has been observed in elderly patients recovered from depression (Porter, *et al*., 2005). Differential effects of ATD on the 3MS have therefore been found in patients with SDAT, remitted depression and PD, but not in healthy older persons, in whom if anything, there is an improvement. To our knowledge, there is no convincing evidence of specific cholinergic deficit in depression in the elderly without PD or dementia. However, a recent study did suggest that cortical cholinergic denervation was associated with depressive symptomatology in PD (Bohnen, *et al*., 2007). It should be noted that in both the recovered depression and in the current study, the significant result was a group by ATD interaction rather than a statistically significant or clinically significant difference in 3MS score in the patient group only. However, it is indicative of a differential effect of ATD between the patient and healthy groups. It is possible that the 3MS is able to pick up subtle changes in performance because, in assessing a broad range of cognitive domains, the number of items assessing different cognitive domains compound to alter performance in a manner not found in tasks with a more specific nature.

The effect seen on IWR involved a reduction in scores during ATD, specific to the PD group with a smaller increase in the control group, neither change reaching statistical significance within the group on post hoc testing. As noted above, previous studies in healthy volunteers and some impaired groups have shown reduced scores on word recall and word recognition during ATD (Sambeth, *et al*., 2007). It is therefore surprising that in the present study this effect was confined to the PD group. The IWR is different from the list learning tasks examined by Sambeth, *et al*. in that the list is presented only once before recognition and the delay is less, presumably altering the relative effects of encoding and consolidation. There are no previously published ATD data for this specific task.

In contrast to the effects on global cognitive function and verbal recognition, the effect on visual recognition memory was reversed. Once again this parallels the results in SDAT where ATD was found to enhance performance on a pattern recognition task (CANTAB PRM), although only in female SDAT patients (Porter, *et al*., 2003). No effects were found on the PRM task in the present study, but a specific interaction was found between ATD and group on a delayed pattern matching task (DMS). It may be that the discrepancy between PRM and DMS is due to the different psychometric properties of different tasks in different patient groups. PRM may be sensitive to performance differences in people with globally impaired cognition but not in the current group, whereas DMS, which involves much more complex stimuli may be more sensitive in individuals without cognitive impairment. Recent imaging and computational modelling studies have demonstrated the involvement of the hippocampus in both visual and verbal recognition memory (Stark and Squire, 2001) and – at least in simulated PRM – this involvement occurs at the 5-HT_{1A} receptor site (Meeter, *et al*., 2006). It is possible given 5-HT_{1A} receptors have an inhibitory function in the hippocampal formation (Yasuno, *et al*., 2003) that in reducing activity at these sites, ATD improved hippocampal function. This would also fit with data suggesting that 5-HT_{1A} antagonists alleviate learning impairment in animal models of dementia (Harder, *et al*., 1996b; Harder and Ridley, 2000; Schechter, *et al*., 2002). It is possible that ATD could facilitate specific aspects of visual learning, in subjects with cholinergic impairment by this mechanism but induce global cognitive impairment by other serotonergic mechanisms.

No effects of treatment were observed in movement as assessed by the UPDRS. This is in accordance with the finding of Scholtissen, *et al*., (2006). However, as noted (Figure 1), there was a group-specific effect of ATD on latency of response on MOT, with patients responding more quickly on the MOT task during ATD. In contrast, Scholtissen and colleagues found all participants, irrespective of diagnosis, were faster during ATD in their not dissimilar SRT but for PD patients, this improvement did not occur on the long interval (i.e., longer interval between interval and response therefore, possibly, higher cognitive load). The SRT used in the Scholtissen, *et al*., study assessed both reaction time and movement time; the participant had to let go the response button on cue (i.e., reaction time) and touch a square shape on a computer screen as quickly as possible (i.e., movement time). They found no treatment by group effect on movement time in this simple task. Nor did they find an effect in a more complicated (compared with SRT) reaction time task – the Finger Precuing Task, which requires the participant to select one of four fingers in response to a precue. The present study also did not find an effect on the more complicated CRT. Together this suggests that ATD has an enhancing effect on reaction time during less demanding tasks and that this effect may also include movement time, particularly because MOT requires a full arm movement to effect a response.

In the present study, ATD was associated with poorer SWM performance across both groups. Findings from studies investigating working memory in younger and older groups have been inconsistent, possibly because the effects of ATD

are relatively subtle. Effects of ATD on SWM have not been demonstrated previously, however, the current study represents a larger overall group (55 participants) than previous studies using this task.

Limitations

The percentage of reduction 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 could detect was 500 ng/mL, which may have artificially elevated the depletion level. A limitation of the study is that we were unable to measure TRP/LNAA ratio and thus, unable to give a more accurate estimate of TRP availability to the brain than free TRP levels. This ratio 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).

A second limitation is that PD patients were *t* of medications. Although serotonergic medications were excluded, patients were on a variety of dopaminergic medications and some were on anticholinergic medications. The load of ingested amino acids given in this procedure was expected to compete with levodopa for absorption in the intestine and entry into the brain. However, because equal loads of amino acids were given on each test session – apart from a relatively small additional amount of tryptophan on the placebo arm – there was likely to be no significant difference in the degree of competition between test sessions. Furthermore, patients took the levodopa 2 h before ingesting the drink allowing most of the absorption of levodopa to occur before any potential interference by the drink.

Conclusion

Overall, the effects of ATD in PD are remarkably subtle and suggest a surprising robustness of this group in the face of a very major reduction in TRP levels. This is in accordance with previous studies in older subjects with presumed serotonergic vulnerability (Porter, *et al*., 2000, 2003; Sambeth, *et al*., 2007) and with previous studies in PD (Leentjens, *et al*., 2006; Scholtissen, *et al*., 2006) in which effects on mood or cognition are either absent or subtle.

However, this study does corroborate previous studies demonstrating a specific sensitivity of older patient groups (SDAT, recovered depression, PD), compared with the healthy elderly to changes in global cognitive status as measured by 3MS during ATD. This may be a factor of an interaction between serotonergic and cholinergic impairment.

The results on the DMS together with previous results on pattern recognition in SDAT provide very preliminary evidence of a beneficial effect of ATD on visual recognition in subjects with cholinergic deficit, which is supported by animal studies (Harder, *et al*., 1996b; Harder and Ridley, 2000; Schechter, *et al*., 2002). This may merit future investigation. Dementia with Lewy bodies and PD with dementia are both associated with a greater cholinergic deficit (Bohnen, *et al*., 2003; Tiraboschi, *et al*., 2000) and may be groups in which these interactions are particularly important.

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