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ORIGINAL INVESTIGATION

R.H. McAllister-Williams · A.E. Massey · M.D. Rugg

Effects of tryptophan depletion on brain potential correlates of episodic memory retrieval

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Abstract *Rationale:* Neuropsychological impairments in depressive illness may be secondary to proposed serotonergic abnormalities. Acute tryptophan depletion (ATD) in healthy subjects impairs episodic memory, but the mechanism of this is unclear. *Objectives:* To examine the effects of ATD on the neural correlates of episodic memory retrieval in healthy subjects. *Methods:* Fourteen healthy men were given an amino acid cocktail drink with or without tryptophan, in a double blind, crossover design. Event related potentials (ERPs) were recorded during a well-validated episodic memory task performed 5 h after drink ingestion. Subjects listened to words spoken in a male or female voice. At test, old and new words were presented visually; subjects judged whether words were old or new, and if old, the gender of the voice at study. *Results:* ATD led to an 84±5% reduction in plasma free tryptophan concentrations, and significantly impaired episodic memory recall. ERP recordings demonstrated previously reported left parietal and right frontal "old/new" differences for ERPs to items associated with accurate episodic memory retrieval versus correctly rejected new items. ATD increased ERP voltage between 500 and 1400 ms post-stimulus particularly over posterior regions of the scalp, but there was no interaction with item type. Topographical analysis of the old/new difference revealed no significant treatment by site interaction. *Conclusions:* ATD impairs episodic memory recall with no effect on the magnitude or topography of the neural correlates of retrieval in healthy subjects. This suggests that the effects of ATD on recall may reflect an impairment of memory encoding and/or consolidation.

R.H. McAllister-Williams (✉) · A.E. Massey
Department of Psychiatry, University of Newcastle,
Newcastle upon Tyne NE1 4LP, UK
e-mail: r.h.mcallister-williams@ncl.ac.uk
Tel.: +44-191-2824034, Fax: +44-191-2275108

M.D. Rugg
Institute of Cognitive Neuroscience and Department of Psychology,
University College London, London WC1N 3BG, UK

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Introduction

Hypotheses of a serotonergic abnormality in depressive illnesses (Ashcroft et al. 1966; Coppen 1967) gain support from the clinical efficacy of selective serotonin reuptake inhibitors (SSRI's; Anderson 1998). The serotonergic system in man has been examined using the technique of acute tryptophan depletion (ATD) which involves a dietary manipulation that lowers plasma and brain tryptophan, and hence 5-HT (for reviews, see Reilly et al. 1997; Moore et al. 2000). ATD leads to a relapse of depressive symptoms in patients who have been treated with SSRIs and are in remission (Delgado et al. 1990). It has also been reported that ATD can lead to a small but significant lowering of mood in healthy subjects (Young et al. 1985); however, this has been disputed by other groups (e.g. Abbott et al. 1992; Oldman et al. 1994). The generally accepted view now is that ATD only lowers mood in vulnerable individuals such as those with a strong family history of depression (Benkelfat et al. 1994; Klaassen et al. 1999) and euthymic subjects on no treatment but with a history of recurrent depression (Smith et al. 1997; Moreno et al. 1999).

Depressed patients show deficits on neuropsychological tests including those connected with learning, memory and executive function (Elliott et al. 1996; Christensen et al. 1997; Goodwin 1997; Veiel 1997; Elliott 1998). It has been argued that these impairments offer an objective means of studying the pathophysiology of depression (McAllister-Williams et al. 1998). The effect of manipulations of the serotonergic system on learning and memory in animals have yielded inconsistent results, with manipulations lowering serotonergic function either impairing, facilitating or having no effect in various paradigms (McEntee and Crook 1991). Some of these inconsistencies may well have resulted from the use of non-specific serotonergic pharmacological probes and a wide variety

of cognitive tests. Gower (1992) concluded that reducing 5-HT activity pre-training impairs performance, whilst the same manipulation made post-training facilitates performance (Gower 1992). In line with this hypothesis, rats fed a low tryptophan diet show impaired learning in an operant discrimination paradigm (Nomura 1992). Likewise, in healthy volunteers, ATD impairs performance in a visual discrimination task only when the ATD is administered on the first session in a cross-over experiment (Park et al. 1994). Schmitt and colleagues (2000) have provided a more robust demonstration that ATD may impair an element of learning or memory other than retrieval of information (Schmitt et al. 2000). Recognition of items in a visual verbal learning test was only impaired for items learnt after, but not before, ATD. On the basis of these findings, Schmitt et al. concluded that ATD specifically impaired episodic memory consolidation.

The neuronal activity underlying episodic memory has been extensively studied by examining event-related brain potentials (ERPs) during a "source memory" task (Wilding and Rugg 1996, 1997a, 1997b). This involves the recollection of details about the encoding context of a recognised item, confirming retrieval of a specific episode. Recollected items elicit ERPs that differ in a characteristic fashion from those elicited both by recognised items allocated to the wrong source, and correctly identified new items in respect of two temporally and spatially distinct components. The left parietal old/new effect consists of a positive-going wave in ERPs to recollected items, which is maximal at left temporo-parietal electrode sites and is seen between approximately 400 ms and 1000 ms post-stimulus. This effect may represent hippocampally modulated cortical activity thought to underlie episodic memory retrieval (Alvarez and Squire 1994; McClelland et al. 1995). The right frontal old/new ERP effect onsets around 400 ms post-stimulus, but it is more sustained over time and is maximal over right frontal scalp regions. It has been suggested that this effect reflects evaluation and monitoring processes, supported by the prefrontal cortex, that operate upon the products of memory retrieval (Wilding and Rugg 1996). The old/new effects are susceptible to pharmacological manipulation in healthy subjects. We have previously demonstrated that repeated administration of cortisol leads to qualitative changes in the magnitude and spatial distribution of these neural correlates of episodic memory retrieval (McAllister-Williams and Rugg 2002).

The aim of the present investigation was to study the effects of ATD on recollection-related ERPs in healthy volunteers. This provides a means to investigate whether, and how, ATD selectively interferes with the cognitive operations underlying episodic memory. In line with previous suggestions that ATD impairs episodic memory consolidation rather than retrieval (Riedel et al. 1999; Schmitt et al. 2000), the hypothesis tested was that ATD would impair source memory recall, but in the absence of attenuated recollection-related ERP effects.

Materials and methods

Subjects

Sixteen right handed healthy male subjects aged between 18 and 31 years (mean age 23) who had English as a first language and provided written informed consent to participate in the study, which had been approved by the local ethics committee. Women were excluded from the study for ethical reasons and due to the extra complications of menstrual cycle interactions with neuropsychological function (Resnick et al. 1998; Man et al. 1999). Two subjects with poor quality EEG recordings and excessive muscular artifacts had to be excluded. All data are therefore reported for the remaining 14 subjects. All were free of significant past or present physical or psychiatric ill health and were receiving no medication. They were excluded if they had a first degree relative with a past history of psychiatric illness. Subjects scored a mean of 0.1±0.5 (mean±SD, range 0–2) on the Hamilton Depression Rating Scale – 21 item (HAMD-21) and 1.6±1.5 (range 0–4) on the Beck Depressive Inventory (BDI). Mean full scale IQ was estimated with the National Adult Reading Test (NART) to be 109±8 (range 98–117).

Study design

Subjects attended the Department of Psychiatry, Royal Victoria Infirmary, Newcastle on two separate occasions at 0900 hours, after an overnight fast, at least 1 week apart. A venous blood sample was obtained, mood rated with the Profile of Mood State (POMS; McNair et al. 1988) questionnaire, and a number of 100 mm visual analogue scales completed by subjects. These included ratings of "depression", "drowsiness", "restlessness", "nausea" and "lightheadedness", with "the most severe possible" at one end and "not at all" at the other. Following these baseline investigations, subjects were given an amino acid drink in a double-blind, random, balanced order. Five hours later, a further blood sample was obtained, POMS and VAS completed, and recollection-related ERPs recorded.

Drink composition

A 100 g amino acid drink was used (Miller et al. 1992), 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 monohydrochoride 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 and L-valine 8.9 g. This was mixed in 300 ml water, flavoured with blackcurrant and sweetened with saccharin. The control drink (T+) also contained 2.3 g L-tryptophan, while the active drink (T–) did not.

Tryptophan assay

Venous blood (10 ml) was taken before the amino acid drink was given and 5 h after ingestion. The blood was added to anticoagulant and the plasma was immediately separated by centrifugation. A sample for free tryptophan was further centrifuged using an ultrafiltrate tube. All samples were stored at –20°C until assay. Plasma total and free tryptophan were determined by high pressure liquid chromatography (HPLC) by the method of Marshall et al. (1987).

Experimental items for ERP procedure

These were identical to material employed in previous studies (Wilding and Rugg 1996; Mark and Rugg 1998) and described by McAllister-Williams and Rugg (2002). Briefly, stimuli consisted of lists of low frequency words (frequency range: 1–7 per million)

selected from the Kucera and Francis corpus (1967). In each list half of the items were spoken in a male voice and half in a female voice, randomly determined. Associated test lists were created with 50% old and 50% new words. Subjects were exposed to two different study/test lists on each of the two recording sessions. At study, the lists of words were presented to subjects binaurally. Test lists of words were presented visually on a computer monitor, with each word presented for 500 ms and subtending a vertical angle of 0.5° and a maximum horizontal angle of 2.8°.

Episodic memory task

Subjects were informed that the aim of the experiment was to investigate memory for spoken words. On each of the two visits subjects underwent an orientation and practice session utilising study and test words not included in the actual experiment. Following the practice, subjects undertook two study/test cycles, as described above.

At study subjects were instructed to listen to each word and to respond verbally by repeating the word aloud and, depending on the gender of the voice, either rating the word as "pleasant/unpleasant" or as "active/passive". As in previous investigations (Mark and Rugg 1998; McAllister-Williams and Rugg 2002), the voice in which each study item was presented dictated which of two encoding tasks should be performed. The mapping of task to gender was counterbalanced across subjects.

Approximately 5 min after the completion of a study list, subjects were presented with the corresponding test list. Subjects were instructed to judge whether each word was one that they had heard in the immediately preceding study task or whether it was new, responding as quickly and accurately as possible by pressing a microswitch under the thumb of one or other hand. For each item that was judged old, subjects were required to wait until cued and then make a judgement, again by pressing one of the two keys, as to whether the word had been spoken in a "male" or "female" voice at study. This indicated whether successful retrieval of a specific episode during the study phase had occurred or not. Note that it is unimportant whether a subject directly recalled the sex of the voice that spoke a word at study or inferred this from recalling how they rated the word during the encoding task. In both cases, successful retrieval of episodic memory has occurred. For each subject, the same response key assignments were maintained for both visits. These assignments were counterbalanced across subjects in order to ensure that there was no correlation between the hands used for old/new and male/female judgements. The total time including the orientation/practice study-test block and two experimental study-test blocks was approximately 45 min.

ERP recording

EEG was recorded from 29 silver/silver chloride electrodes positioned on the scalp using an elasticated cap (Easy Caps, Germany) and sited in accordance with the International 10–20 system (American Electroencephalographic Society 1994). Further electrodes were placed on the right and left mastoid processes. All channels were recorded relative to the left mastoid, and ERPs were algebraically reconstructed off-line to represent recordings with respect to an average mastoid reference. Vertical EOG was recorded between electrodes placed on the nazion and electrodes below the centre of the right and left eyes. Horizontal EOG was recorded between electrodes placed on the outer canthus of the left and right eyes. EEG and EOG were filtered with a bandpass of 0.01–30 Hz and sampled at a rate of 6 ms per point for an epoch of 1536 ms beginning 102 ms before test stimulus onset.

ERPs were formed for each subject for recognised old items attracting correct source judgements, and for correctly identified new items. To maximise the number of trials available to form the ERPs, a blink-correction procedure was employed to remove the blink EOG artefact from concurrently recorded EEG. Trials containing EOG artefact originating from eye-movements other than blinks were rejected, as were trials on which baseline drift exceeded 55 μV, or on which there was saturation of the A/D converters, in any channel. To maintain an acceptable signal/noise ratio, a lower limit of 20 artefact-free trials per subject per visit per response category was set.

Statistical analysis

All values are quoted as means±SD. Statistical comparisons were made using analysis of variance (ANOVA) incorporating the Geisser-Greenhouse correction for inhomogeneity of covariance, with *F* ratios reported with corrected degrees of freedom.

Results

Tryptophan concentrations

Complete sets of plasma samples were not available for two subjects due to difficulties with venipuncture. As a result data are quoted from the remaining 12 subjects. Following the T– drink, plasma total and free tryptophan concentrations were reduced by 85.6±3.9% and 84.4±5.1%, respectively. Conversely, the T+ drink increased total and free tryptophan concentrations by 64.7±51.8% and 71.3±57.9%, respectively. These findings are in line with previous studies using a similar amino acid mixture (Reilly et al. 1997).

Mood and VAS

In line with other studies examining the effects of ATD in individuals with low baseline depression scores, no previous history of depression and an absence of a family history of depressive illnesses, there was no significant effect of ATD on any of the POMS sub-scales (Reilly et al. 1997). In addition, there was no significant effect of ATD on any of the VAS scales except nausea, which was significantly higher following the T+ versus the T– drinks [$F(1,13)=9.02$, $P<0.01$].

Behavioural data

A previous study using identical study and test stimuli found no significant effect of the sex of the voice on response accuracy or speed (Wilding and Rugg 1996). Consequently, all behavioural analysis was performed on data collapsed across sex of voice speaking the items at study. In line with previous studies (Wilding and Rugg 1996; Mark and Rugg 1998; McAllister-Williams and Rugg 2002), trials in which words were correctly judged new will be referred to as "correct rejections", and new words judged to be old as "false alarms". Trials in which words were correctly judged to be "old" are referred to as "hits", and if correctly assigned to their study context as "hit/hits". Analysis of the behavioural data focused on two measures: recognition, as assessed by the discrimination index (probability of a "hit" minus the probability

of a “false alarm”; Snodgrass and Corwin 1988) and probability of correct source judgement given recognition (indicating episodic recall, or “source memory”). Subjects' performance is shown in Fig. 1. ANOVA employed a within-subject factor of treatment (T– versus T+ drinks) and a between-subject factor of the visit the T– drink was administered (first versus second). Unlike a previous cross over study using identical stimuli (McAllister-Williams and Rugg 2002), no significant effect of visit was found on either recognition or source memory. ATD had a non-significant effect on recognition [T–: 0.74±0.13; T+: 0.78±0.10; $F(1,12)=1.57$, $P>0.1$], but significantly impaired source memory [T–: 0.79±0.10; T+ 0.83±0.09; $F(1,12)=5.04$, $P<0.05$].

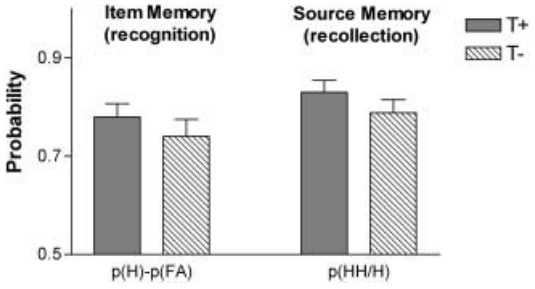

Fig. 1 Effect of ATD on item and source memory. Item memory is defined as the probability of a correct recognition of an old item (hit) minus the probability of the subjects falsely reporting a new item as old (false alarm; Snodgrass and Corwin 1988). Source memory is defined as the probability of a correct source judgement for items correctly recognised

Response times (RTs) for the initial recognition responses for both correct rejections and recollected old items (hit/hits) were analysed using an ANOVA with within-subject variables of response type (correct rejections or hit/hits) and treatment, and a between-subject variable of the visit the T– drink was administered. This demonstrated no effect of ATD, visit or response type on RTs.

Event-related potential analysis

Only ERPs elicited by correct rejection and hit/hit items were analysed. All other response types occurred with a frequency that was too low to provide sufficient numbers of trials to generate reliable average ERP waveforms. Previous work using the same stimuli found no effect of the sex of the study voice on the ERP wave forms in line with a lack of effect on the behavioural responses; (Wilding and Rugg 1996) and so ERPs were collapsed across study voice.

Grand averages of the ERPs for the hit/hit and correct rejection response categories from the 14 subjects following treatment with the T+ drink are illustrated in Fig. 2, while Fig. 3 illustrates ERPs after the T– drink. The ERPs shown in both Fig. 2 and Fig. 3 demonstrate the same pattern of “old/new” effects as reported previously

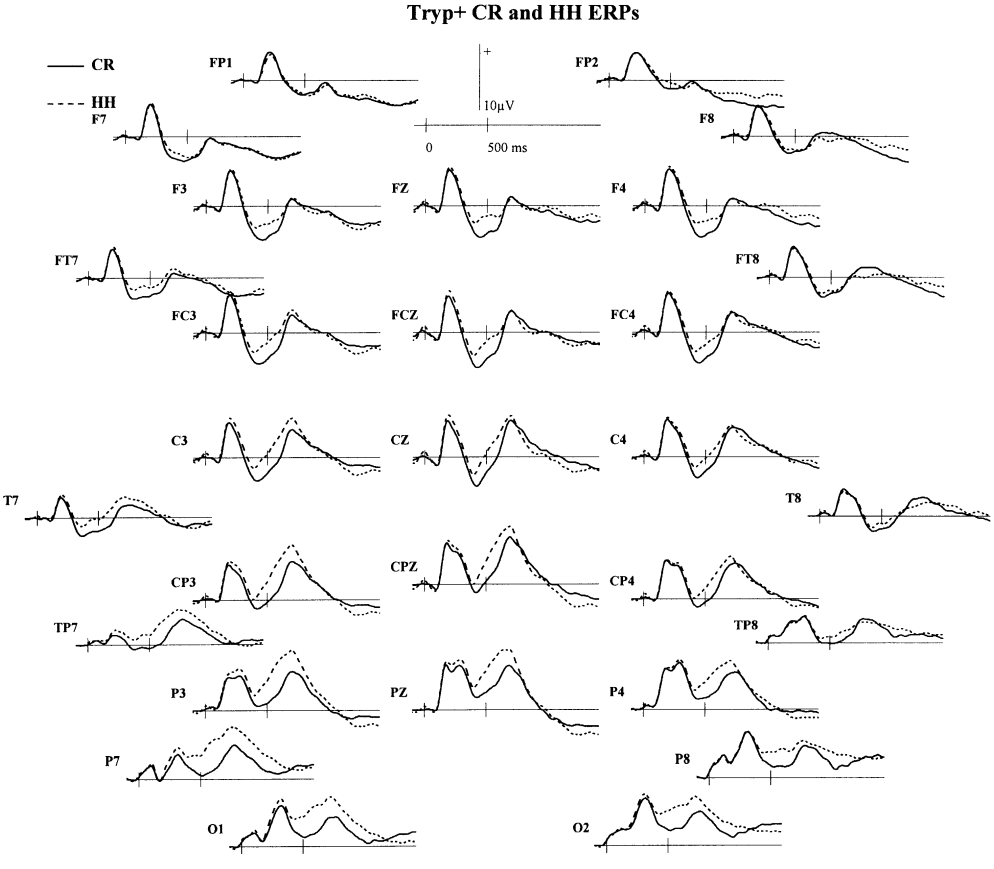

Fig. 2 Correct rejection (*CR*) and hit/hit (*HH*) ERP grand average waveforms following control T+ drink. Correct rejection ERPs are shown with a *solid line*, while hit/hit ERPs are shown with a *dashed line*. The electrode sites are laid out as if looking from above with the front of the head at the top

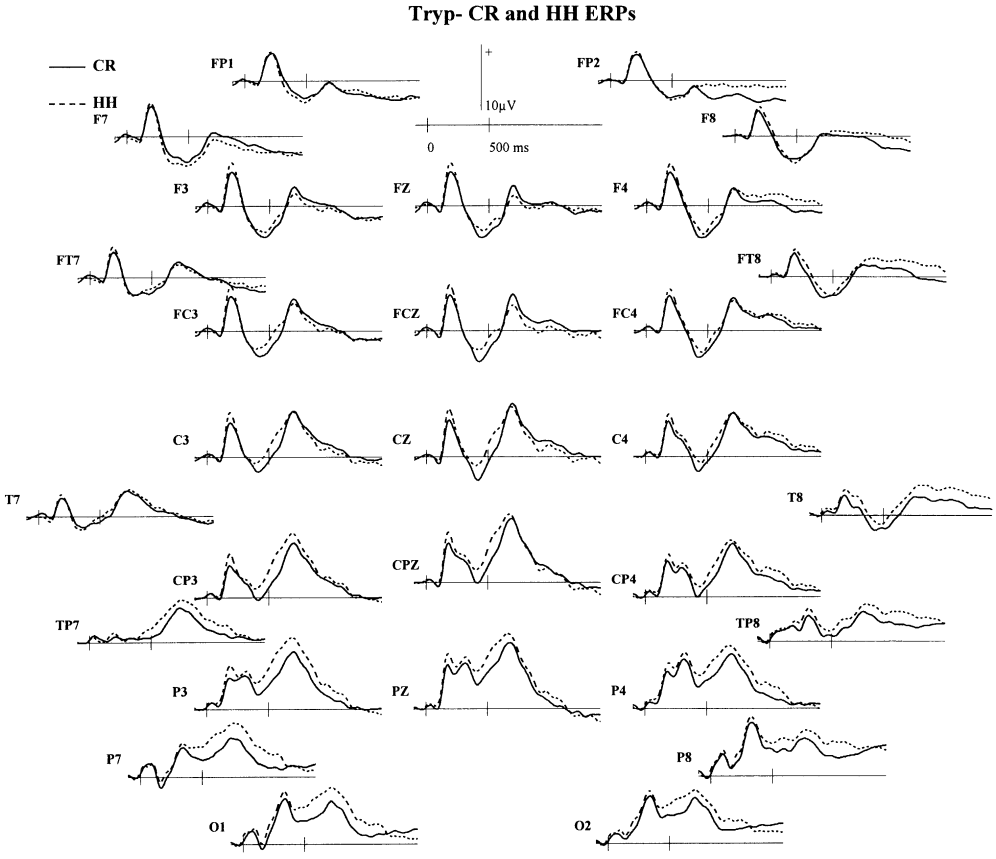

Fig. 3 Correct rejection (*CR*) and hit/hit (*HH*) ERP grand average waveforms following ATD with the T– drink. All other details are as described for Fig. 2

(Wilding and Rugg 1996; Mark and Rugg 1998; Rugg et al. 1998). From around 400 ms post stimulus, the hit/hit ERP is relatively more positive going than the correct rejection ERP. This difference is larger over the left temporo-parietal region than the right, but is larger over right than left frontal sites. Figure 4A, where the correct rejection waveforms from each condition are overlaid, shows correct rejection ERPs to be more positive following the T– than the T+ drink across the scalp, but particularly posteriorly. A similar pattern is seen with the hit/hit waveforms (Fig. 4B). Given that the magnitude of the effect of ATD appeared to be similar on both correct rejection and hit/hit ERP waveforms, little effect of ATD was seen on the "old/new" ERP difference (Fig. 4C).

A priori, it was decided to quantify the ERP data by measuring, with respect to the mean of the pre-stimulus baseline, the mean amplitudes of three consecutive latency regions, 500–800, 800–1100 and 1100–1400 ms post-stimulus, as done previously (Wilding and Rugg 1996; Mark and Rugg 1998; Rugg et al. 1998; McAllister-Williams and Rugg 2002). For each latency region the data were analysed in two ways. First an ANOVA was conducted on data from the three central electrodes (Fz, Cz and Pz), employing the factors of treatment (T– versus T+ drinks), response type (hit/hit versus correct rejection) and electrode site. Second an ANOVA was conducted on four clusters of electrodes, three each in the left anterior (FP1, F7 and F3), right anterior (FP2, F8 and F4), left posterior (O1, P7 and P3) and right posterior quadrants (O2, P8 and P4) chosen a priori on the basis of previous data demonstrating the old/new effect (Wilding and Rugg 1996). Analysis of these four clusters employed the factors of treatment, response type, hemisphere (left versus right), location (anterior versus posterior), and electrode site.

In addition to the ANOVAs described above, further analyses were conducted on the data from all electrode sites to assess the effects of ATD on the topography of the ERP old/new effects. These analyses were conducted on the amplitude differences between the hit/hit and correct rejection waveforms for each of the three latency periods described above, after the data had been re-scaled to remove global differences in amplitude (McCarthy and Wood 1985).

Analysis of mean amplitudes

Analysis of mean amplitudes is detailed in Table 1. Analysis of the three central sites demonstrated a significant effect of response for the 500–800 ms region, with hit/hits being more positive than correct rejections. A trend for a main effect of drug was found for all three time periods due to the waveforms being more positive after the T– drink compared to the T+ drink. A significant treatment by site interaction between 500 and 800 ms reflected a greater effect of ATD at Pz compared to Fz. No significant treatment by response interaction was found for any of the time periods indicating a similar effect of ATD on both correct rejection and hit/hit ERP waveforms.

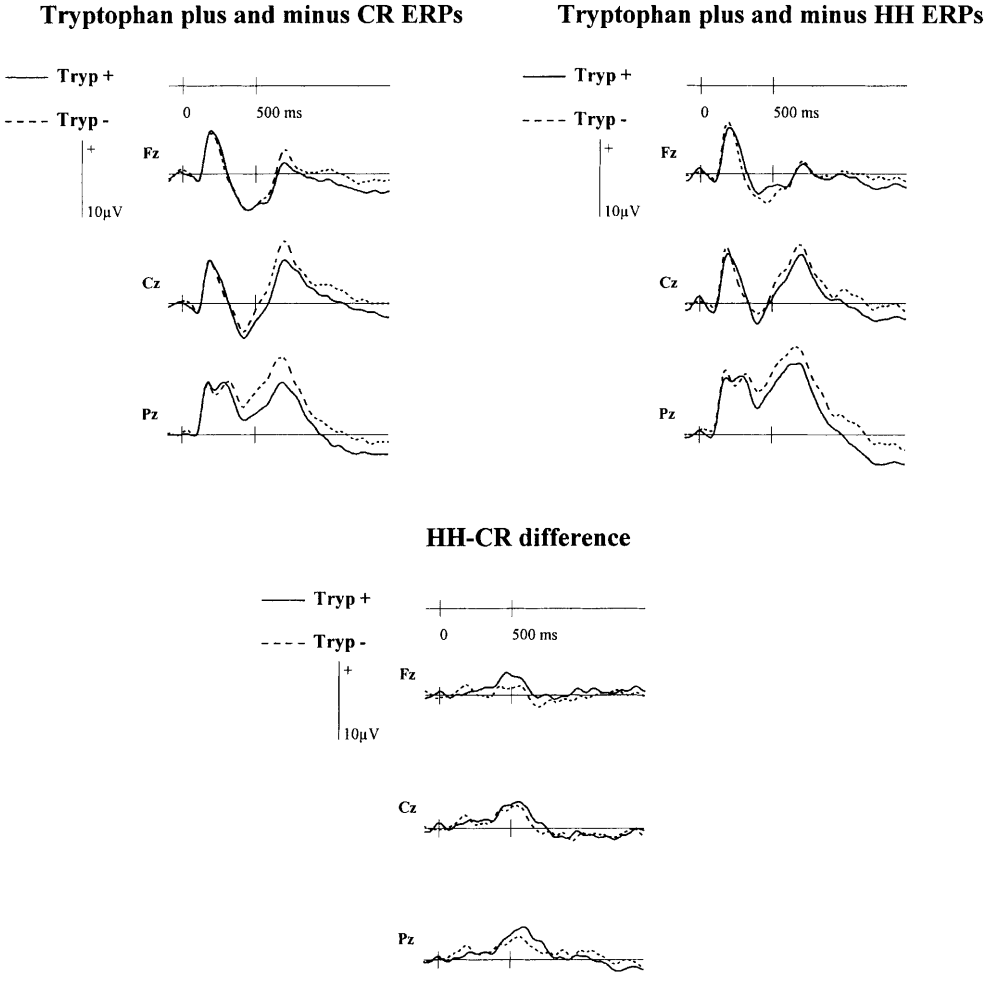

Fig. 4 Grand average waveforms and subtraction waveforms from three midline sites. **A** Waveforms elicited by correct rejections following T+ (*solid line*) and T– (*dashed line*) drinks. **B** Waveforms elicited by hit/hit responses following T+ (*solid line*) and T– (*dashed line*) drinks. **C** Old/new ERP effect (hit/hit minus correct rejection waveforms) following T+ (*solid line*) and T– (*dashed line*) drinks

Table 1 Analysis of ERP mean amplitudes. The ANOVA results of analysis of the mean ERP waveforms recorded at three central electrode sites (Fz, Cz, Pz) and four clusters of three electrodes in the left anterior (FP1, F7 and F3), right anterior (FP2, F8 and F4), left posterior (O1, P7 and P3) and right posterior quadrants (O2, P8 and P4). *CR* correct rejection of new item

		500–800 ms	800–1100 ms	1100–1400 ms
Three central sites	Effect of response (hit/hit vs CR)	3.20 vs 2.20 μV [$F(1,13)=5.59$, $P<0.05$]	NS	NS
	Effect of treatment (T+ vs T–)	2.18 vs 3.23 μV [$F(1,13)=3.48$, $P<0.1$]	0.37 vs 1.33 μV [$F(1,13)=3.15$, $P<0.1$]	–1.49 vs –0.29 μV [$F(1,13)=4.01$, $P<0.1$]
	Treatment×Response	NS	NS	NS
	Treatment×Site	$F(1.4,17.9)=7.45$, $P<0.01$	NS	NS
Four lateral clusters	Effect of response (hit/hit vs CR)	2.08 vs 1.15 μV [$F(1,13)=11.80$, $P<0.005$]	1.25 vs 0.52 μV [$F(1,13)=3.69$, $P<0.1$]	NS
	Response×Location (anterior vs posterior)×hemisphere	$F(1,13)=6.78$, $P<0.05$	$F(1,13)=6.52$, $P<0.025$	$F(1,13)=11.16$, $P<0.005$
	Effect of treatment (T+ vs T–)	NS	0.58 vs 1.19 μV [$F(1,13)=3.82$, $P<0.1$]	–0.67 vs 0.08 μV [$F(1,13)=5.33$, $P<0.05$]
	Drug×Response	NS	NS	NS
	Drug×Hemisphere	NS	NS	NS
	Drug×Location	$F(1,13)=5.64$, $P<0.05$	NS	NS
	Drug×Response×Location×Hemisphere	NS	NS	NS

Analysis of the four clusters of lateral electrode sites revealed a significant main effect of response type between 500 and 800 ms and a trend for an effect between 800 and 1100 ms. In addition, significant response by location (anterior versus posterior) by hemisphere interactions were found in all three time regions, reflecting the left temporo-parietal and right frontal "old/new" effects. A main effect of ATD was found between 1100 and 1400 ms with waveforms being more positive after the T– than T+ drink and a trend for this effect was observed

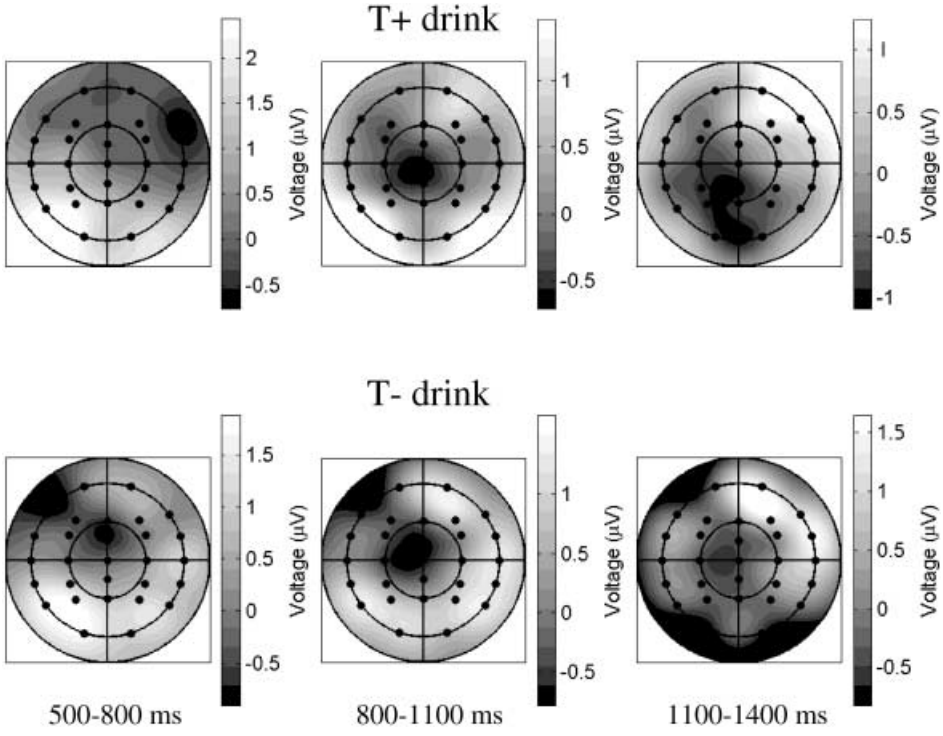

Fig. 5 Spherical spline maps illustrating the scalp topography of the differences between ERPs to hit/hits and correct rejections following control T– drink (*upper row*) and ATD with the T+ drink (*lower row*) for the latency periods indicated

between 800 and 1100. In line with the treatment by site interaction for the three central sites between 500 and 800 ms, analysis of the four lateral clusters revealed a treatment by location interaction in the same time period, again indicating a greater effect of ATD posteriorly. However no significant treatment by response or treatment by response by location by hemisphere interactions were found indicating that ATD had no effect on the magnitude of the old/new effects.

Topographic analysis

Topographic analysis revealed no significant effect of ATD on the topography of the old/new effects. No treatment by site interaction was found for all 29 active electrode sites for any of the three time periods. Likewise, analysis of the three central sites also found no treatment by site interaction and analysis of the four lateral clusters revealed no treatment by location, treatment by hemisphere or treatment by location by hemisphere interaction. The topography of the old/new effects following both the T– and T+ drinks are illustrated graphically by means of spherical spline maps for all three latency periods in Fig. 5.

Discussion

This is the first study to investigate the effect of ATD on the neural correlates of episodic memory retrieval. ATD led to a large and significant reduction in plasma total and free tryptophan. This was not associated with any lowering of mood. ATD significantly impaired episodic memory recall, but in the absence of any significant change in either the magnitude or topography of the electrophysiological correlates of episodic retrieval.

The degree of lowering of free and total tryptophan seen in this study is in line with previous published reports of the use of identical amino acid mixtures (Reilly et al. 1997). Plasma tryptophan levels are lowered due to stimulation of protein synthesis following ingestion of the amino acid cocktail. Together with competition from other large neutral amino acids (LNAAs) for transport across the blood-brain barrier, brain tryptophan, and hence 5-HT, concentrations are lowered. It has been shown that an 80–90% reduction in plasma free tryptophan (as found in this study) correlates with an equal or greater reduction in CSF tryptophan (Carpenter et al. 1998) and a 90% reduction in brain 5-HT synthesis (Young et al. 1999). One potential confound of the ATD procedure used here is that the control drink (which contains tryptophan) leads to an increase in plasma tryptophan concentrations. Central 5-HT concentrations reflect the ratio of plasma tryptophan to other LNAAs. Using identical drinks to the ones used here, a previous study in schizophrenic patients conducted in our laboratories has shown that while the T– drink significantly lowers the tryptophan concentration relative to LNAAs, the T+ drink had no effect on this ratio (Golightly et al. 2001). An additional confound is that tyrosine also competes with tryptophan for the same transporter into the brain. Lowering tryptophan may increase central tyrosine, and hence dopamine concentrations (Reilly et al. 1997). However, it has been shown that the tyrosine to LNAA ratio is unaffected by either drink (Golightly et al. 2001).

This suggests that the T+ drink used in this study is an appropriate control.

The subjects recruited into this study had notably low depression ratings as assessed using the Hamilton Depression Rating Scale and the Beck Depressive Inventory. They were also rigorously screened to exclude any that had a family history of a first degree relative who had suffered from depression. The lack of any effect of ATD on the mood of these subjects is consistent with the current view that ATD does not induce a lowering of mood in healthy subjects (Moore et al. 2000; Reilly et al. 2000). The effects seen here on episodic memory recall are therefore not secondary to lowered mood.

It has previously been shown that ATD impairs paired associate tests of visuo-spatial memory (Park et al. 1994) and delayed recall and recognition memory in an auditory verbal learning task (Riedel et al. 1999). The current finding of impaired source memory is consonant with these findings, though no significant impairment in recognition (item memory) was found. This latter finding may reflect the fact that simple recognition memory judgements can be supported by non-episodic memory ("familiarity", e.g. Aggleton and Brown 1999). Alternatively, the dissociation between recognition and source memory may merely reflect the relative difficulties of these two judgements. The impairment of recall in the absence of any effect on the magnitude or topography of the neural correlates of retrieval is consistent with hypotheses that ATD impairs aspects of memory other than retrieval (Schmitt et al. 2000). These may include processes of consolidation and encoding. Effects of ATD on one or both of these processes cannot be differentiated with the current experimental design and further studies are required to clarify this issue.

While no effect of ATD was seen on the magnitude or topography of the old/new effects, ATD did lead to increased positivity in the ERP waveforms, this effect having a posterior scalp distribution. As the effect was independent of the stimulus type (old or new word), this finding suggests that ATD may exert effects on brain function related to the demands of the experimental task generally, but unrelated to specific aspects of retrieval processing. Increased positivity of posteriorly distributed ERPs was also seen following repeated cortisol administration to healthy volunteers in an analogous study of episodic memory retrieval (McAllister-Williams and Rugg 2002). This finding was interpreted as possibly reflecting processes underlying the speeding of RTs that was seen with the cortisol treatment. However, in the current experiment, no change in RTs was found (indeed, previous studies have found delayed recognition RTs with ATD (Riedel et al. 1999). Furthermore, a direct comparison of the topographies of the effects from the previous and present experiment suggests that the two effects reflect the activity of different neural populations [ANOVA on hit/hit waveforms from each study employing a between-subject factor of study and within-subject factors of epoch (500–800, 800–1100 and 1100–1400 ms post stimulus) and electrode site (29 scalp locations) revealed a trend towards a study by electrode site interaction, $F(6.0,155.9)=1.89$, $P<0.1$)]. Thus, there is no obvious explanation of the effect of ATD on ERPs observed in the present study. Its interpretation would be aided by further studies that investigate whether the effect is found only during memory related tasks of the kind employed here, or is evident in tasks engaging non-mnemonic cognitive operations also.

On the basis of a number of animal experiments, Richter-Levin and Segal (1996) have concluded that reduced serotonergic function in the hippocampus contributes to age-associated memory deficits. In this regard, it is of particular note that the findings we have made here are strikingly similar to a study comparing elderly with young healthy subjects using an identical ERP paradigm (Mark and Rugg 1998). This study found that source memory (recollection) was impaired in the elderly compared to younger subjects, with item memory (recognition) being intact. Furthermore, there was no age-related difference in the magnitude or topography of the left parietal or right frontal old/new ERP effects. The similarity of these findings with those made in the current study support the hypothesis of Richter-Levin and Segal of a role of 5-HT impairment in age related memory decline. This clearly warrants further investigation.

Serotonergic abnormalities have also been postulated to underlie depressive illnesses (Ashcroft et al. 1966; Coppen 1967), as have impairments in the hypothalamic-pituitary-adrenal (HPA) axis that include raised cortisol concentrations (Murphy 1991; Dinan 1994). An abnormality in either system may underlie the neuropsychological impairment seen in depression (McAllister-Williams et al. 1998). We have previously shown that repeated cortisol administration has a significant effect on the magnitude and topography of recollection ERPs, with an impairment in recognition and a speeding of RTs in healthy subjects (McAllister-Williams and Rugg 2002). The very different profile of the effects of cortisol compared to ATD provides a means of examining which of these systems may be responsible for the neuropsychological impairment seen in depression. Consequently, we are currently recording recollection-related ERPs in a cohort of antidepressant free depressed patients and matched healthy controls.

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