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Review

Effects of tryptophan loading on human cognition, mood, and sleep

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ABSTRACT

Modulating central serotonergic function by acute tryptophan depletion (ATD) has provided the fundamental insights into which cognitive functions are influenced by serotonin. It may be expected that serotonergic stimulation by tryptophan (Trp) loading could evoke beneficial behavioural changes that mirror those of ATD. The current review examines the evidence for such effects, notably those on cognition, mood and sleep. Reports vary considerably across different cognitive domains, study designs, and populations. It is hypothesised that the effects of Trp loading on performance may be dependent on the initial state of the serotonergic system of the subject. Memory improvements following Trp loading have generally been shown in clinical and sub-clinical populations where initial serotonergic disturbances are known. Similarly, Trp loading appears to be most effective for improving mood in vulnerable subjects, and improves sleep in adults with some sleep disturbances. Research has consistently shown Trp loading impairs psychomotor and reaction time performance, however, this is likely to be attributed to its mild sedative effects.

Contents

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1. Introduction

1.1. Serotonin

Serotonin (5-hydroxytryptamine; 5-HT) is a monoamine neurotransmitter, responsible for neurochemical signal transduction between neurons. The neurons of the raphe nuclei are the principal source of 5-HT release in the brain. Although there are relatively few serotonergic neurons in the brain, these neurons innervate widespread areas of the brain, such as the forebrain, hippocampus, cerebellum and spinal cord (Haider et al., 2006), and are considered important in the modulation of several essential behavioural and physiological functions, such as mood, sleep and wakefulness, cognition, sexual behaviour, appetite, aggression, impulsivity, neurodevelopment, circadian rhythms, body temperature, and neuroendocrine function (Jacob and Fornal, 1995).

Reduced 5-HT function is recognised as a contributing factor in affective disorders, such as depression, bipolar disorder, anxiety disorders, and obsessive compulsive disorder (Davis et al., 2002). Medicinal drugs that stimulate 5-HT activity throughout the brain, predominantly selective serotonin reuptake inhibitors (SSRIs) and various tricyclic antidepressants (TCAs), are effective in ameliorating the symptoms of these disorders. Furthermore, cognitive deficits that frequently accompany these disorders have also been shown to improve with pro-serotonergic pharmacological therapies (Schmitt et al., 2006).

1.2. Modulation of serotonergic function by dietary tryptophan

For a limited number of neurotransmitters, such as serotonin, dietary precursors can influence the rate of synthesis and function of the neurotransmitters. The synthesis of 5-HT is dependent on the brain availability of its precursor, the amino acid L-tryptophan (Trp). The amino acid is converted via a short metabolic pathway consisting of the two enzymes tryptophan hydroxylase and amino acid decarboxylase to serotonin. Tryptophan hydroxylase, the rate-limiting enzyme on the pathway from Trp to 5-HT, is not normally saturated with Trp. Thus, increasing Trp levels can increase 5-HT synthesis as much as twofold following 3 g pure Trp load (Young, 1996; Young and Gauthier, 1981), which is significant to modulate mood, cognition and behaviour (Attenburrow et al., 2003; Cunliffe et al., 1998; Marsh et al., 2002; Markus et al., 2008; Yuwiler et al., 1981). While decreasing Trp availability can cause a considerable decline in 5-HT synthesis and turnover (Nishizawa et al., 1997).

Trp is transported across the blood–brain barrier by a specific active transport system, which also transports a number of other large neutral amino acids (LNAAs: leucine, isoleucine, tyrosine, phenylalanine, and valine) into the brain. As a result, Trp competes with these other LNAAs for active transport sites. Therefore, the uptake of Trp does not depend on total concentration of plasma Trp alone, but primarily on the plasma ratio of Trp to the sum of other LNAAs (Trp–LNAA ratio) (Fernstrom and Wurtman, 1972). An increase in the plasma Trp–LNAA ratio can result in an increased uptake of Trp in the brain. Thus, the relative amount of LNAAs in the diet has a major impact on the levels of Trp in the brain. A diet high in Trp, but with a large amount of LNAAs, will not result in higher brain Trp levels, and may even decrease Trp uptake into the brain. An intervention rich in Trp relative to other LNAAs is needed in order to boost uptake of Trp, and consequently serotonin production, in the brain.

1.3. Increasing brain tryptophan

Increases in plasma Trp–LNAA ratio can be achieved by giving Trp the advantage in competition for access to the brain (Fernstrom and Wurtman, 1971), either through the intake of pure Trp (Markus et al., 2008; Sobczak et al., 2002, 2003), increasing carbohydrate intake (Fernstrom and Wurtman, 1971, 1972; Markus et al., 1998), or through consumption of tryptophan-rich α-lactalbumin protein (Markus et al., 2000, 2002). Throughout the review these methods of increasing brain Trp will be referred to as Trp loading.

α-Lactalbumin is a whey-derived protein with the highest Trp content and highest Trp–LNAA ratio of all food protein sources (Heine et al., 1996). α-Lactalbumin has been shown to increase plasma Trp–LNAA ratio up to 130% (Booij et al., 2006; Markus et al., 2000, 2005; Merens et al., 2005; Scrutton et al., 2007). Ingestion of normal protein, which also contains Trp, decreases brain Trp. This is because Trp is the least abundant amino acid in protein, and therefore the increase in plasma Trp is less than the increase in plasma LNAAs that compete with Trp for transport into the brain. Carbohydrates, on the other hand, which contain no Trp, increase brain Trp and 5-HT, due to a carbohydrate-induced rise in glucose, which triggers insulin secretion. Insulin stimulates the uptake of LNAA in skeletal muscles, with the exception of Trp (Fernstrom and Wurtman, 1971). Consequently, LNAA plasma levels fall, competition for the transport of Trp decreases, and brain levels of Trp and 5-HT increase. However, a carbohydrate rich/protein poor (CR-PP) diet increases plasma Trp–LNAA ratio (20–25%; Markus et al., 1998, 1999) considerably less than α-lactalbumin.

For the purpose of the present review, the effects of Trp loading in humans (clinical populations, vulnerable volunteers, and healthy volunteers) on cognitive function, mood, and sleep are considered, to explore the potential benefits of serotonergic stimulation through Trp loading. As previously mentioned, brain Trp can be increased through intake of either pure Trp, a carbohydrate rich/protein poor diet, or α-lactalbumin. Therefore, studies employing these Trp loading manipulations are discussed.

2. Methods

2.1. Selection procedures

An extensive medline search was performed from 1966 to January 2009 using the search terms: "tryptophan", "α-lactalbumin", "cognition", "memory", "attention", "vigilance", "executive function", "emotional processing", "mood", and "sleep". The search was limited to human studies only. The bibliographies of the references identified were searched for additional papers that met the following inclusion criteria: (1) original papers written in English appearing in a peer-reviewed journal, (2) include a comparison condition (Trp loading versus placebo or ATD), (3) specify sample characteristics for the participants, (4) include cognitive, mood and/or sleep assessments. All studies that assessed Trp loading on cognition, mood and/or sleep meeting the above criteria were included in the review.

2.2. Methodological remarks

Forty-three studies were identified for inclusion in the review. Sixteen studies assessed the effects of Trp loading on cognitive functioning. Thirteen articles assessed the effects of Trp loading on mood, and 21 studies assessed the effects of Trp loading on sleep measures. Twenty-three studies included only healthy subjects, 8 studies assessed healthy volunteers and vulnerable populations (i.e. mental illness, participants with family history of mental illness, stress-prone, premenstrual women, individuals with sleep disturbances), and 12 studies included only vulnerable populations. Thirty-one studies increased brain Trp with pure Trp. Nine studies increased brain Trp with α-lactalbumin, and three studies increased brain Trp with a carbohydrate rich/protein poor diet. The Trp loading studies included in the review are summarized in Tables 1–3.

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Table 1
Summary of cognitive findings.

Study	Subjects	Dose	Increase from baseline in plasma Trp–LNAA ratio	Intervention type	Measures	Results
Luciana et al. (2001)	19 healthy adults	10.3 g L-Trp	Not available; total plasma Trp levels increased by tenfold from 53.22 to 551.4 μmol/L	Acute, repeated-measures, double-blind design (no placebo – Trp loading or depletion)	Spatial working memory; affective working memory; verbal fluency; sustained attention and short-term memory span; motor speed and accuracy	Decrements in working memory for verbal and affective stimuli relative to Trp depletion; decrements in motor performance; improved sustained attention; no effect on mood
Morgan et al. (2007)	8 healthy adults	30 mg/kg body weight L-Trp	Not available	Acute, repeated-measures, double-blind, placebo-controlled design	Executive function	No effects found
Attenburrow et al. (2003)	24 healthy females	Nutritionally sourced pure Trp (1.8 g Trp)	Not available	Acute, double-blind, parallel group, placebo-controlled design	Emotional processing	Trp enhanced perception of fearful and happy facial expressions relative to placebo
Murphy et al. (2006)	38 healthy adults	14 days Trp intervention of 1 g three times a day	Not available	Sub-chronic, double-blind, parallel group, placebo-controlled design	Emotional processing (facial expression recognition, emotion-potentiated startle, attentional probe, emotional categorisation and memory); mood	Trp increased the recognition of happiness and decreased recognition of disgust in females; Trp decreased attentional vigilance towards negative stimuli and reduced baseline emotional startle response in females; no effects on mood
Scrutton et al. (2007) (10)	28 healthy females	40 g α-lactalbumin-rich drink (total Trp level 1.8 g)	80%	Acute, double-blind, parallel group, placebo-controlled design	Emotional processing; mood	No effects found; increase in subjective rating of nausea 150 min after α-lactalbumin ingestion
Winokur et al. (1986)	11 healthy males	5, 7.5 and 10 g L-tryptophan; saline administered intravenously		Acute, repeated-measures, double-blind, placebo-controlled design	Psychomotor performance; subjective ratings of fatigue	L-Trp produced a dose-dependent impairment in motor performance; L-Trp increased mental and physical sedation, but did not alter subjective ratings of tranquilization
Cunliffe et al. (1998) (11)	6 healthy adults	30 mg/kg body weight L-Trp	41% (peak)	Acute, repeated-measures, double-blind, placebo-controlled design	Subjective measure of fatigue (VAS), objective measure of central fatigue (Flicker Fusion Frequency task), simple reaction time, peripheral fatigue (grip strength and wrist ergometry)	Trp decreased performance on the Flicker Fusion Frequency task (measure central fatigue); Trp slowed reaction time performance; Trp increased subjective ratings of fatigue
Dougherty et al. (2007)	18 healthy adults	5.15 g Trp	127%	Acute, repeated-measures, double-blind, placebo-controlled design	Sustained attention, impulsivity	Trp loading produced fewer errors of omission during a vigilance task in the Trp loading condition relative to the Trp depletion condition
Markus et al. (2005) (7)	Healthy subjects with (n = 14) or without (n = 14) mild sleep complaints	40 g (2 × 20 g) tryptophan-enriched α-lactalbumin protein (4.8 g/100 g Trp)	130% increase from placebo	Repeated-measures, double-blind, placebo-controlled design	Subjective sleepiness; vigilance; EEG (ERPs)	α-Lactalbumin reduced sleepiness in the morning, improved morning alertness and attention (P300 ERP) in both groups; α-lactalbumin improved next morning vigilance performance in subjects with mild sleep complaints
Markus et al. (2002) (4)	23 high stress-vulnerable and 29 low stress-vulnerable subjects	40 g α-lactalbumin-rich drink (2 × 20 g containing 12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%)	Not available; Trp–LNAA ratio was 43% greater after α-lactalbumin diet than after control diet	Acute, repeated-measures (diet), between-subject, double-blind design	Memory scanning	Improved memory scanning in high stress-vulnerable subjects compared to placebo; no effect of Trp in low stress-vulnerable subjects
Markus et al. (1999)	22 high stress-vulnerable and 21 low stress-vulnerable subjects (aged 19–26 yrs)	Carbohydrate rich/protein poor diet versus protein rich/carbohydrate poor diet	Not available	Acute, repeated-measures (diet), between-subject, double-blind design	Memory scanning	Improved memory scanning after experimental stress only in high-stress volunteers with carbohydrate rich/protein poor diet

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Table 1 (*Continued*)

Study	Subjects	Dose	Increase from baseline in plasma Trp–LNAA ratio	Intervention type	Measures	Results
Markus et al. (1998) (5)	24 high stress-Vulnerable and 24 low stress-vulnerable subjects (aged 18–25 yrs)	Carbohydrate rich/protein poor diet versus protein rich/carbohydrate poor diet	Not available; Trp–LNAA ratio increased 48% in the carbohydrate rich/protein poor diet from the protein rich/carbohydrate poor diet	Acute, repeated-measures (diet), between-subject, double-blind design	Memory scanning; mood	Failed to demonstrate memory scanning improvements following a carbohydrate rich/protein poor diet in stress-prone subjects following experimental stress although basic reaction speed was increased in pooled groups; in high stress subjects a carbohydrate rich/protein poor diet prevented deterioration of feelings of depression and vigour during stress manifested after protein rich/carbohydrate poor diet
Schmitt et al. (2005) (1)	16 Females with premenstrual symptoms	40 g α-lactalbumin-rich drink (2 × 20 g containing 12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%)	6–25%	Acute, repeated-measures, double-blind, placebo-controlled design	Short- and long-term memory; executive function	Improved long-term memory for abstract figures, but not for words; no effect on executive function
Sayegh et al. (1995) (2)	24 Premenstrual females with PMS	Carbohydrate rich drink	29%	Acute, repeated-measures, double-blind, placebo-controlled design	Verbal recognition memory; verbal retrieval; mood	Improved verbal recognition memory; decreased self-report measures of depression, anger, confusion
Sobczak et al. (2003, 2002) (9)	30 healthy first-degree relatives of bipolar patients and 15 matched controls	7 g Tryptophan intravenous	Trp–LNAA ratio increased 1500% as baseline ratio was 0.11 and 105 min after Trp ratio was 1.835	Acute, between-group, repeated-measures, double-blind, placebo-controlled design	Planning; sustained attention; focused attention; divided attention; response inhibition; psychomotor performance; short- and long-term memory; verbal fluency; mood	Trp impaired long-term memory retrieval and storage and decreased movement time on a psychomotor task in both groups; Trp impaired focused attention and planning in subjects with first-degree relative with bipolar disorder; Trp increased feelings of anger, depression, fatigue, tension, and decreased feelings of vigour and feelings of alertness in both groups relative to placebo
Booij et al. (2006) (3)	23 recovered depressed patients (21 F and 2 M) and 20 controls (17 F and 3 M)	40 g α-lactalbumin-rich drink (2 × 20 g containing12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%)	21%	Acute, repeated-measures, double-blind, placebo-controlled design	Short- and long-term memory; focused attention and response inhibition; motor speed; executive function; mood	Improved abstract visual memory, in both recovered depressed patients and healthy controls; slowed motor response in both groups; no effect on mood or other cognitive functions

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Table 2
Summary of mood findings.

Study	Subjects	Dose	Increase from baseline in plasma Trp–LNAA ratio	Intervention type	Measures	Results
Luciana et al. (2001)	19 healthy adults	10.3 g L-Trp	Not available; total plasma Trp levels increased by tenfold from 53.22 to 551.4 μmol/L	Acute, repeated-measures, double-blind design (no placebo – Trp loading or depletion)	Mood; spatial working memory; affective working memory; verbal fluency; short-term attention and memory span; motor speed and accuracy	No effect on mood; decrements in working memory for verbal and affective stimuli relative to rp depletion; decrements in motor performance; improved sustained attention
Markus et al. (2008) (8)	18 healthy subjects	15 g α-lactalbumin whey-protein with 0.8 g Trp and 9.4 g LNAA (Trp–LNAA ratio 0.1); hydrolysed protein (Pep2Balance) with 0.8 g Trp and 4 g LNAA (Trp–LNAA ratio 1.1); 0.8 g pure Trp; and 1.2 g synthetic peptide containing 0.8 g Trp; 20 g casein protein with 0.4 g Trp and 10 g LNAA (Trp–LNAA ratio 0.04)	α-Lactalbumin–67% Pep2balance–255% pure Trp–191% synthetic peptide–263%	Acute, repeated-measures, double-blind, placebo-controlled design	Mood and plasma amino acids	Hydrolysed protein (Pep2Balance™) produced faster and greater increases in plasma Trp–LNAA ratio compared to α-lactalbumin and pure Trp; Mood improved 60 min after consumption hydrolysed protein and pure Trp. Most profound and durable mood enhancing effects observed 210 min after intake of hydrolysed protein. No mood effects observed with α-lactalbumin or synthetic Trp peptide
Murphy et al. (2006)	38 healthy adults	14 days Trp intervention of 1 g 3 times a day	Not available	Sub-chronic, double-blind, parallel group, placebo-controlled design	Mood; emotional processing (facial expression recognition, emotion-potentiated startle, attentional probe, emotional categorisation and memory)	No effects on mood; Trp increased the recognition of happiness and decreased recognition of disgust in females; Trp decreased attentional vigilance towards negative stimuli and reduced baseline emotional startle response in females
Scrutton et al. (2007) (10)	28 healthy females	40 g α-lactalbumin-rich drink (total Trp level 1.8 g)	80%	Acute, double-blind, parallel group, placebo-controlled design	Mood; emotional processing;	No effects found; increase in subjective rating of nausea 150 min after α-lactalbumin ingestion
Beulens et al. (2004) (12)	18 healthy males	12 g α-lactalbumin-enriched whey-protein (Trp–LNAA ratio of 0.16) with carbohydrates versus carbohydrates only	16%	Acute, repeated-measures, double-blind, placebo-controlled design	Mood	No effects
Yuwiler et al. (1981)	5 healthy males	50 mg/kg L-Trp acute; 100 mg/kg L-Trp acute; 50 mg/kg L-Trp sub-chronic for 14 days	Not available	Repeated-measures, double-blind design	Mood and alertness	No effect of Trp on valence of mood; Trp increased lethargy and drowsiness within 30 min after 50 mg/kg L-Trp ingestion
Markus et al. (1998) (5)	24 high stress-Vulnerable and 24 low stress-vulnerable subjects (aged 18–25 yrs)	Carbohydrate rich/protein poor diet versus protein rich/carbohydrate poor diet	Not available; Trp–LNAA ratio increased 48% in the carbohydrate rich/protein poor diet from the protein rich/carbohydrate poor diet	Acute, repeated-measures (diet), between-subject, double-blind design	Mood; memory scanning	In high stress subjects a carbohydrate rich/protein poor diet prevented deterioration of feelings of depression and vigour during stress manifested after protein rich/carbohydrate poor diet; failed to demonstrate memory scanning improvements following a carbohydrate rich/protein poor diet in stress-prone subjects following experimental stress

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Table 2 (*Continued*)

Study	Subjects	Dose	Increase from baseline in plasma Trp–LNAA ratio	Intervention type	Measures	Results
Markus et al. (2000) (6)	29 high stress-Vulnerable and 29 low stress-vulnerable subjects	40 g α-lactalbumin-rich drink (2 × 20 g containing12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%)	Not available; Trp–LNAA ratio increased 48% after α-lactalbumin diet from the control diet	Acute, repeated-measures (diet), between-subject, double-blind, placebo-controlled design	Mood	α-Lactalbumin-rich diet reduced depressive symptoms in stress-vulnerable subjects after experimental stress
Sayegh et al. (1995) (2)	24 Premenstrual females with PMS	Carbohydrate rich drink	29%	Acute, repeated-measures, double-blind, placebo-controlled design	Mood; verbal recognition; memory; verbal retrieval	Decreased self-report measures of depression, anger, confusion; Improved verbal recognition memory
Steinberg et al. (1999)	80 females with premenstrual dysphoric disorder	6 g L-Trp (given as 2 g three times a day) for 17 days	Not available	Sub-chronic, between-subject, randomised, double-blind, placebo-controlled design	Mood	L-Trp more effective than placebo in controlling extreme mood swings, dysphoria, irritability, and tension
Sobczak et al. (2003, 2002) (9)	30 healthy first-degree relatives of bipolar patients and 15 matched controls	7 g Tryptophan intravenous	Trp–LNAA ratio increased 1500% as baseline ratio was 0.11 and 105 min after Trp ratio was 1.835	Acute, between-group, repeated-measures, double-blind, placebo-controlled design	Mood; planning; sustained attention; focused attention; divided attention; response inhibition; psychomotor performance; short- and long-term memory; verbal fluency	Trp increased feelings of anger, depression, fatigue, tension, and decreased feelings of vigour and feelings of alertness in both groups relative to placebo; Trp impaired long-term memory retrieval and storage and decreased movement time on a psychomotor task in both groups; Trp impaired focused attention and planning in subjects with first-degree relative with bipolar disorder
Merens et al. (2005) (13)	23 recovered depressed adults and 20 healthy adults	40 g α-lactalbumin-rich drink (2 × 20 g containing12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%)	21%	Acute, repeated-measures, between-subject, double-blind, placebo-controlled design	Mood	α-Lactalbumin had no effect in improving mood after experimental stress
Booij et al. (2006) (3)	23 recovered depressed patients (21 F and 2 M) and 20 controls (17 F and 3 M)	40 g α-lactalbumin-rich drink (2 × 20 g containing 12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%)	21%	Acute, repeated-measures, double-blind, placebo-controlled design	Mood; short- and long-term memory; focused attention and response inhibition; motor speed; executive function	No effect on mood; improved abstract visual memory in both recovered depressed patients and healthy controls; slowed motor response in both groups

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Table 3
Summary of sleep findings.

Study	Subjects	Dose	Increase from baseline in plasma Trp–LNAA ratio	Intervention type	Measures	Results
Wyatt et al. (1970) (1)	Healthy adults	7.5 g Trp	Not available		Sleep parameters	Trp decreased REM sleep and increased non-REM sleep
Nicholson and Stone (1979) (2)	6 healthy males	2, 4, and 6 g L-Trp	Not available		Sleep parameters	4 g L-Trp increased percentage of REM sleep and duration of stage 3 daytime sleep; no modulations to sleep found during nighttime sleep following 2, 4, and 6 g L-Trp
Hartmann et al. (1974) (3)	Healthy adults	1–15 g Trp (dose–response study)	Not available		Sleep parameters	1–15 g Trp decreased sleep latency, but only in doses above 5 g modulations to sleep stages observed, specifically, decreases in desynchronised sleep % increases in slow-wave sleep
Leatherwood and Pollet (1984) (19)	Healthy adults	500 mg Trp (5 nights)		Sub-chronic, double-blind, repeated-measures, placebo-controlled design	Sleep parameters	Trp decreased sleep latency, sleep depth increased, increased sleepiness, and calming effects were reported; younger females more sensitive to the sedating effects of Trp than any other group
George et al. (1989) (6)	10 healthy adults	1.2 or 2.4 g L-Trp	Not available	Acute, repeated-measures, double-blind, placebo-controlled design	Objective (sleep latency) and subjective measures of sleepiness and their relationship to blood L-Trp levels	Both L-Trp doses reduced sleep latency at 1 h, with reduction persisting at 2 h for 2.4 L-Trp only; positive correlation between subjective and objective sleepiness measures for 2.4 g dose only; correlation between blood Trp and sleep latency found at 0, 60 min and 120 min for both doses
Spinweber et al. (1983) (8)	20 healthy adults	4 g L-Trp	Not available; however plasma total Trp levels increased 260% and free Trp 343% relative to placebo	Acute, repeated-measures, double-blind, placebo-controlled design	Waking EEG and daytime sleep	L-Trp reduced sleep latency without altering nap sleep stages; during waking EEG L-Trp increased alpha latency, theta latency, theta amplitude, and decrease alpha frequency; conclusion L-Trp effective sleep hypnotic
Thorleifsdottir et al. (1989) (15)	20 healthy adults	2 g L-Trp	Not available	Acute, repeated-measures, double-blind, placebo-controlled design	Daytime arousal measured with EEG	Trp increased drowsiness reflected by increases in theta amplitude and decreases in alpha amplitude; subjective ratings of sleepiness increased with Trp; psychomotor performance not affected with Trp
Chauffard-Alboucq et al. (1991) (20)	9 healthy females	500 mg and 1 g L-Trp combined with a carbohydrate load	200% (500 mg) 300% (1 g)	Acute, double-blind, repeated-measures, placebo-controlled design	Perceived sleepiness; sedative effects	Both Trp doses increased sleepiness and sedative effects relative to placebo. Effect was observed when plasma Trp–LNAA ratio increased 200% (500 mg) and 300% (1 g) from baseline, peaking 90 minu after Trp administration. Peak in perceived sleepiness found 90 min after Trp consumption
Körner et al. (1986) (7)	10 adults with sleep disturbances	5 g L-Trp	Not available	Acute, repeated-measures, double-blind, placebo-controlled design	Sleep parameters	Trp decreased sleep latency, improved sleep period time and total sleep time; no effect on slow-wave sleep
Brown et al. (1979) (5)	18 females with laboratory sleep-onset latency greater than 20 min	1 g or 3 g L-Trp for 10 nights	Not available	Sub-chronic, repeated-measures, double-blind, placebo-controlled design	Sleep parameters	Trp had no effect on amount of REM, slow-wave sleep and wakefulness relative to placebo; reductions in sleep-onset latency with 3 g Trp
Hartman and Spinweber (1979) (9)	15 mild insomniacs	250 mg, 500 mg and 1 g L-Trp	Not available	Acute, repeated-measures, double-blind, placebo-controlled design	Sleep parameters	1 g Trp reduced sleep latency, whereas the lower Trp doses produced trends in same direction; Stage IV sleep increased with 250 mg Trp
Hudson et al. (2005) (10)	57 chronic insomniacs	25 mg deoiled butternut squash seed meal (contains 22 mg Trp/1 g protein) mixed with 25 mg dextrose; 250 mg pharmaceutical Trp mixed with 25 mg dextrose and 25 g rolled oats; rolled oats (placebo)	Not available	Acute, between-subjects, double-blind, placebo-controlled design	Objective (total sleep time, sleep efficiency, total wake time, time awake-middle of the night) and subjective (overall perceived quality) measures of sleep	Protein source Trp and pharmaceutical grade Trp improved subjective and objective sleep measures
Hartman et al. (1983) (11)	96 chronic insomniacs	1 g L-Trp; 100 mg secobarbital; 30 mg flurazepam; placebo for 7 days	Not available	Sub-chronic, between-subjects, double-blind, placebo-controlled design	Sleep parameters	Trp did not improve sleep during treatment phase (7 days), however post-treatment Trp improved sleep latency

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Table 3 (*Continued*)

Study	Subjects	Dose	Increase from baseline in plasma Trp–LNAA ratio	Intervention type	Measures	Results
Demisch et al. (1987a) (13)	39 chronic insomniacs	2 g L-Trp and 0.04 g L-Trp (instead of placebo)	Not available	Acute, repeated-measures, double-blind design	Sleep parameters	Full L-Trp (2 g) dose administered first improved sleep relative to low Trp dose. However, when low Trp dose administered first, no difference found between two treatment conditions. Authors argue that L-Trp seems to be effective in promoting sleep in subjects with chronic insomnia
Demisch et al. (1987b) (14)	25 chronic insomniacs	2 g L-Trp for 4 weeks and 4 weeks no treatment	Not available	Sub-chronic, repeated-measures, double-blind design	Sleep parameters	Trp improved sleep patterns; subjective sleep ratings improved with Trp; sleep deteriorated in only half of the patients during the control period (no treatment)
Spinweber (1986) (4)	20 male chronic sleep-onset insomniacs	3 g L-Trp (6 nights)	Not available	Sub-chronic, between-subject, double-blind, placebo-controlled design	Sleep; performance; arousal; brain electrical activity	No effect of L-Trp on sleep latency during first three nights of administration; nights 4–6 sleep latency reduced; no effect on sleep stages; Trp did not impair performance; Trp elevated arousal threshold; Trp did not alter brain electrical activity
Schneider-Helmert (1981) (12)	8 severe insomniacs	2 g L-Trp (3 nights) followed by 4 night placebo period	Not available	Sub-chronic, repeated-measures, double-blind, placebo-controlled design	Sleep parameters	Improvements to sleep found to continue during a four night placebo period compared to the pre-Trp baseline, suggesting interval therapy to be useful method in cases of severe insomnia
Aparicio et al. (2007) (18)	18 healthy infants	Standard infant commercial milk (1.5% Trp) administered during daytime and nighttime for 1 week; second condition Trp enriched milk (3.4% Trp) given during light-time (06:00–18:00) and standard commercial milk given during nighttime (18:00–06:00) for 1 week; experimental condition infants received the standard commercial milk during daytime and Trp enriched milk during nighttime for 1 week	Not available	Sub-chronic, double-blind, repeated-measures design	Sleep patterns	Infants receiving low Trp formula during the day and high Trp formula during the night, slept more, manifested better sleep efficiency, increased immobility time, had fewer night movements and waking episodes. No statistical differences found between two control groups despite the fact that quite different amounts of Trp were administered (1.5% and 2.72%). Conclusion: milk formulas with varying Trp contents that are appropriate to light–dark variations improve the sleep/wake cycles of infants who are not breast fed
Yogman and Zeisal (1983) (16)	20 healthy newborn infants (2–3 days old)	Trp in 10% glucose or valine in 5% glucose	Not available	Acute, between-subjects design	Sleep patterns	Newborns fed Trp had shorter sleep latencies, and entered rapid eye movement and quiet sleep sooner than when fed commercial formula
Steinberg et al. (1992) (17)	57 healthy infants	Formula containing 0, 294, 588, 882 μmol/L of added Trp; for comparative purposes standard human milk and commercial formula included	Plasma Trp–LNAA ratio greatest for infants fed human milk (0.132) and formula containing highest level of added Trp (0.129)	Sub-chronic, randomised, between-subjects design	Sleep patterns	Trp–LNAA ratio, not plasma Trp concentrations, predicted differences in sleep latency across the different treatment conditions. Sleep latency was shorter for infants with the highest Trp–LNAA ratios. Infants consuming formulas with lower Trp loading had sleep latencies similar to those of infants consuming commercial formula. Infants consuming highest Trp dose sleep latencies were shorter than for infants in the human milk-fed condition. Infants fed high dose of Trp tended to be less alert, spent less time crying, and more time sleeping than infants fed lower levels of added Trp
Harada et al. (2007)	1055 infants (0–6 months), 751 young children (0.6–8 years), and 473 older children (9–15 years)	No intervention; index of Trp calculated at breakfast	Not available	Naturalistic study design	Sleep habits and mental symptoms (e.g. depression, anger)	Positive correlation between Morning–Evening scores and Trp index for infants and young elementary children; lower Trp index scores associated with increased levels of difficulty in infants falling asleep at bedtime and waking up in the morning

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3. Effects of tryptophan loading on cognitive function

In the past decades, animal and human experiments have provided evidence that central 5-HT can modulate a wide array of cognitive processes, although the specific actions of 5-HT on distinct cognitive (sub) domains remains somewhat elusive. Much of the evidence is derived from psychopharmacological manipulations that increase or decrease 5-HT activity in the brain, either globally or via specific 5-HT receptors. An overview of the vast literature on animal studies investigating the role of 5-HT on cognition is beyond the scope of this paper. Several excellent reviews have recently been published on this topic (e.g. Monleon et al., 2008; Meneses, 2007a; Meneses and Perez-Garcia, 2007b; King et al., 2008; Fone, 2008).

In humans, most data originate from studies that have used acute tryptophan depletion (ATD) to induce an acute global reduction in 5-HT synthesis in the brain, or from studies using acute or sub-chronic administration of pro-serotonergic drugs, mostly antidepressants. Detailed recent reviews are available on the effects of ATD on human cognitive functioning (Mendelsohn et al., 2009) and human brain activation (Anderson et al., 2008; Evers et al., 2007; Fusar-Poli et al., 2006), as well as on the findings of pro-serotonergic drug research (Schmitt et al., 2006; Merens et al., 2007; Harmer, 2008). Studies examining the cognitive effects of 5-HT stimulation by TRP loading on human cognitive performance provide additional information on the role of 5-HT in human cognitive performance and these studies are reviewed (see Table 1). In the following sections, the TRP loading results for each of the investigated cognitive domains are discussed in the context of the relevant findings from human ATD and pro-serotonergic drug studies.

3.1. Tryptophan loading and memory

Research indicates that 5-HT is involved in specific memory processes. The most compelling evidence for this in humans has been obtained from ATD studies showing impaired long-term memory functioning following ATD. These seem to be specifically related to disturbed consolidation of new information in the long-term memory. The effects of ATD are most robustly observed in visual verbal learning tests, where delayed recall and/or recognition is impaired (Mendelsohn et al., 2009; Schmitt et al., 2006). However, a recent pooled analysis of nine ATD studies (Sambeth et al., 2007) revealed that ATD also impairs immediate recall, potentially through disruption of early consolidation and/or impairment of encoding of new information. The impairing effects were more pronounced in women. No consistent ATD-induced impairments were found on short-term or working memory (Mendelsohn et al., 2009). As for serotonergic stimulation, studies employing acute or sub-chronic administration of serotonergic drugs (i.e. SSRIs, 5-HT receptor agonists) in healthy volunteers show an inconsistent pattern of no effects, impairments and improvements of various memory functions (Schmitt et al., 2006). Although in depressed patients, successful serotonergic pharmacotherapy is generally associated with cognitive enhancement, the direct effects of 5-HT on memory and other cognitive functions cannot be easily disentangled from potential cognitive enhancement through alleviation of other depressive symptoms (mood, motivation and sleep disturbances) (see Schmitt et al., 2006).

A total of eight studies have examined the memory effects of Trp loading, with four measuring effects on long-term memory functioning. Sobczak et al. (2003) reported memory deficits following Trp loading in healthy adults and in healthy first-degree relatives of bipolar patients. Specifically, impairments in delayed word recall and recognition were found following an intravenous 7 g Trp challenge. However, the high dose of Trp (which increased plasma Trp–LNAA ratio by 1500%) also produced significant sedative effects that were apparent from the subjective rating scores. Moreover, sedation was positively correlated with memory decrements, suggesting that the memory impairment may be attributed to melatonin accumulation, a neuro-hormone that regulates the circadian cycle by chemically causing drowsiness and thus promoting sleepiness (Richardson, 2005; Vanecek, 1998, see Section 6).

During the premenstrual stage, women with premenstrual complaints manifest serotonergic abnormalities (Halbreich, 2003; Kouri and Halbreich, 1997), which may underlie, at least partially, certain symptoms, such as memory deficits (Schmitt et al., 2005). Interestingly, 40 g α-lactalbumin (plasma Trp–LNAA ratios increased between 6% and 25% from baseline) or a carbohydrate rich drink (Trp–LNAA increased ratio by 29%) resulted in improvements in long-term memory for abstract figures and long-term memory word recognition, respectively, in women with premenstrual complaints during the premenstrual stage (Sayegh et al., 1995; Schmitt et al., 2005).

In a more recent study, exploring the effects of Trp loading on cognitive performance in unmedicated recovered depressed patients and matched controls, Booij et al. (2006) found that an α-lactalbumin-rich diet (two chocolate drinks each containing a whey-protein fraction rich in α-lactalbumin; containing 12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%) improved abstract visual memory (specifically, recognition and speed of retrieval from short- and long-term abstract visual memory), without affecting mood, in healthy controls and in recovered depressed subjects (plasma Trp–LNAA ratio increased 21% from baseline). These results indicate that the beneficial effects of Trp loading on memory are not limited to individuals vulnerable to 5-HT related disorders. Moreover, these findings are consistent with the ATD literature where memory consolidation deficits have been observed in healthy volunteers (Riedel et al., 1999; Schmitt et al., 2000). However, the beneficial effects of Trp loading on memory performance may be attributed to impaired memory performance that was observed in the placebo (casein) condition. Without a non-intervention control group this possibility cannot be negated. However, the change in plasma Trp–LNAA ratio in the casein condition is comparable to previous findings (Merens et al., 2005; Schmitt et al., 2005) and justifies the use of casein as a placebo.

The other four studies focused on working memory performance changes after Trp loading. Luciana et al. (2001) compared the effects of Trp loading with the effects of Trp depletion on various cognitive processes in healthy subjects. 10.3 g L-Trp loading increased total plasma Trp by tenfold (53.22 at baseline to 551.4 μmol/L), and resulted in decrements to working memory performance for verbal and affective stimuli relative to Trp depletion. As both Trp loading and Trp depletion resulted in decreased levels of positive affect, the authors argue that the memory impairments in the Trp loading condition are not likely to be attributed to changes in mood. However, as there was no placebo condition the results are difficult to interpret and may be inflated.

Improvements in short-term memory scanning have been observed in stress-vulnerable subjects following acute Trp loading (Markus et al., 1999, 2002). Increased serotonergic activity is an established consequence of stress (Joseph and Kennett, 1983; Stanford, 1993), and continual stress may lead to a shortage of the supply of this neurotransmitter. Consequently, serotonin activity may drop below the functional levels producing stress-related cognitive disturbances. In accordance with this, it would be expected that Trp loading would improve cognitive performance in stress-prone subjects following acute stress as the diminished serotonergic pools are replenished by Trp loading. Consistent with this, Markus et al. (1999) found short-term memory scanning

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improvements, following laboratory acute stress, only in high stress-prone volunteers after a carbohydrate rich/protein poor diet. In low stress-vulnerable subjects, Trp loading had no effect on cognitive performance, as the serotonergic system was not compromised to begin with. Further support for the beneficial effects of Trp loading in high stress-prone subjects was found in a later study where increases in plasma Trp, following an α-lactalbumin-rich diet (two chocolate drinks each containing a 20 g whey-protein fraction rich in α-lactalbumin; containing 12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%), were shown to improve memory scanning ability in healthy, stress-vulnerable subjects (Markus et al., 2002). As expected, and consistent with the previous study, this effect was not observed in the control group (low stress-vulnerable subjects) (Markus et al. (2002). Interestingly, in an earlier study Markus et al. (1998) failed to show improvements to short-term memory following a carbohydrate rich/protein poor diet in stress-prone subjects following laboratory stress. Although the diet significantly increased the plasma Trp–LNAA ratio by 42%, no memory scanning effects were found. The authors suggested that the lack of effects may be attributable to a higher level of the subject's control of the induced stress (Markus et al., 1999).

Hitherto, no studies addressing the chronic effects of Trp on human cognitive function have been performed. However, animal studies have produced some interesting results. In a recent study, it was shown that following 6 weeks of oral Trp administration (100 mg/kg body weight), spatial working memory was improved in Trp-treated rats (Haider et al., 2006). Similarly, Khaliq et al. (2006) reported improved memory following 6 weeks oral administration of Trp at doses of 50 and 100 mg/kg body weight in rats. At both doses plasma Trp, brain Trp, and 5-HT levels increased with Trp. The authors concluded that increases in brain 5-HT synthesis following long-term Trp administration may be involved in the observed memory enhancement. Haider et al. (2007) reported improvements in short- and long-term memory and in learning acquisition following 6 weeks administration of Trp at doses 50 and 100 mg/kg body weight in rats. These results further indicate that long-term administration of Trp as a dietary supplement may be beneficial to memory functioning. Future work should assess whether chronic consumption of Trp similarly improves memory function in humans.

In summary, improvements in long-term memory processes, memory scanning ability, and abstract visual memory following Trp loading have been shown in vulnerable and clinical populations where some serotonergic disturbances are known (i.e. females with premenstrual symptoms, recovered depressed patients, and in stress-vulnerable subjects following experimental stress). In contrast, in healthy volunteers the reports are inconsistent.

3.2. Tryptophan loading and attention

Sustained attention (vigilance) refers to the ability to direct and focus attention or alertness to a task over a prolonged period of time. There is consistent evidence from a series of studies with serotonergic antidepressants that 5-HT stimulation (acute and sub-chronic) impairs vigilance performance in healthy volunteers as measured by the Mackworth Clock Test (Riedel et al., 2005; Wingen et al., 2008; for review see Schmitt et al., 2006). In contrast, ATD generally does not affect sustained attention (Mendelsohn et al., 2009) as measured by a variety of tasks (although not the Mackworth Clock Test). Two studies have assessed the effects of Trp loading on sustained attention. Both Luciana et al. (2001) and Dougherty et al. (2007) observed fewer errors of omission during a vigilance task in the Trp loading condition (10.3 g L-Trp; 5.15 g Trp, respectively) relative to the Trp depletion condition, in healthy adults. These results suggest that Trp loading may improve sustained attention. However, as there was no placebo condition and results were compared only to Trp depletion, the results may be inflated.

Focused or selective attention refers to the ability to attend to relevant stimuli while simultaneously ignoring irrelevant information. ATD studies have provided evidence for 5-HTs involvement in focused attention (Mendelsohn et al., 2009; Schmitt et al., 2006). ATD has been shown to reduce interference on the Stroop test (a frequently employed measure of focused attention, response inhibition, and cognitive flexibility) and increase performance on focused attention components of dichotic listening tasks in healthy and depressed subjects (Booij et al., 2005; Rowley et al., 1998; Schmitt et al., 2000). Further substantiation for 5-HTs role in focused attention is found in ATD studies employing electrophysiological measures in healthy subjects (Ahveninen et al., 2002).

The few studies that have explored the effects of 5-HT loading on focused attention (Go/NoGo Task, Stroop Colour Word Test, Left/Right Choice Reaction Time, Dichotic Listening Task) have shown minimal effects. A 7 g intravenous Trp challenge resulted in performance decrements on the Go/NoGo Task and a Left/Right Choice Reaction Time task in subjects with a first-degree relative with bipolar disorder (Sobczak et al., 2003), which is consistent with the effects of ATD on focused attention. Although the deficit in focused attention could be explained by a corresponding sedative effect produced by the high Trp dose, a similar deficit in focused attention was not observed in the healthy control group. In addition, the impairment did not extend to other tests of focused attention (i.e. the Stroop test and dichotic listening). This is consistent with Booij et al. (2006) who reported no effects of α-lactalbumin (2×20 g whey-protein containing 12.32 g/kg Trp; Trp–LNAA ratio increase from baseline 21%) on the Stroop task in both recovered depressed patients and healthy controls.

There is no clear indication that Trp loading affects sustained or focused attention, although the data on both functions are scarce. No data are available on Trp loading effects on divided attention.

3.3. Tryptophan loading and executive functions

Executive functions is a general term that refers to a wide variety of cognitive processes such as planning, decision-making, monitoring and behavioural adaptation, reasoning, cognitive flexibility, and response inhibition (Chan et al., 2008). These functions are considered essential for purposeful, goal-directed, future-oriented behaviour.

Serotonin's contribution to executive functioning processes remains unclear. ATD studies have produced inconsistent results across most of the executive function domains. Although some treatment effects have been reported for planning ability, cognitive flexibility and decision-making (Murphy et al., 2002; Park et al., 1994; Rogers et al., 1999, 2003; Sobczak et al., 2002; Talbot et al., 2006), a considerable amount of research has shown no effects of ATD on planning, cognitive flexibility, decision-making abilities, response inhibition, and attentional set-shifting or reversal learning (Anderson et al., 2003; Booij et al., 2005; Evers et al., 2004, 2005; Gallagher et al., 2003; Hughes et al., 2003; LeMarquand et al., 1998; Roiser et al., 2007, 2008; Talbot et al., 2006).

Trp loading has not been shown to modulate planning or response inhibition in healthy adults (Booij et al., 2006; Morgan et al., 2007; Sobczak et al., 2003). Furthermore, in sub-group and clinical populations, Trp loading has similarly not modulated planning or response inhibition (Booij et al., 2006; Schmitt et al., 2005). However, Sobczak et al. (2003) observed significant decrements in planning functions (assessed with the Tower of London task) in healthy first-degree relatives of bipolar patients

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following an intravenous 7 g Trp challenge, which was not observed in the control group. Interestingly, planning deficits have previously been reported in healthy first-degree relatives of bipolar patients following acute tryptophan depletion (Sobczak et al., 2002), which could suggest that these patients may be sensitive to any modulations to serotonergic functioning.

Overall, Trp loading – as well as ATD studies – has not shown clear evidence of serotonergic modulation of the various aspects of executive functioning. Although this may indicate 5-HT does not exert a meaningful influence on these functions, the inconsistencies may also be partly related to more general issues regarding executive function test sensitivity and reliability, particularly in repeated assessments where the level of novelty may confound the test outcomes (Rabbitt, 1997; Chan et al., 2008).

3.4. Tryptophan loading and emotional processing

Over past years, there has been an increasing interest in the role of serotonin in processing and classifying emotionally loaded information. Emotional processing is typically assessed by measuring response biases to positive or negative stimuli (words, pictures, reward, punishment) in attention, memory or reaction time tests, or by measuring perception and classification of emotionally loaded stimuli, such as emotional face expressions. Evidence for a serotonergic involvement in such processes has emerged, as human studies have shown that ATD can decrease recognition of facial emotions, particularly for fearful expressions, and leads to a response bias towards negative stimuli in healthy volunteers and vulnerable populations (Harmer, 2008), although an absence of ATD effects on facial recognition has also been reported (Cools et al., 2005; Fusa-Poli et al., 2007; Van der Veen et al., 2007). Serotonergic stimulation by acute SSRI administration produces generally opposite effects of those seen with ATD and enhances positive affective processing (see Harmer, 2008; Merens et al., 2007 for detailed overviews).

Although the number of studies is limited, the results suggest that Trp loading can modulate emotional information processing using facial emotion recognition tasks. Attenburrow et al. (2003) investigated the acute effects of pure Trp (1.8 g Trp) loading on facial expression recognition in healthy females. The authors found that Trp enhanced the perception of fearful and happy facial expressions relative to placebo. Consistent with this, Murphy et al. (2006), reported increases in the recognition of happiness and decreases in the recognition of disgust in healthy females following 14 days Trp intervention (1 g three times a day). Furthermore, Trp administration decreased attentional vigilance towards negative stimuli and reduced the baseline emotional startle response. These effects were not seen in males. Interestingly, modulations of emotional processing were observed in the absence of any change in subjective mood ratings. Thus, the authors argue that the decrease in attentional vigilance towards negative stimuli is a direct consequence of modulations to 5-HT levels in the brain that is independent to mood improvement.

In contrast, Scrutton et al. (2007) failed to find an effect of 40 g α-lactalbumin-rich drink (total Trp 1.8 g) on recognition of emotional facial expressions in healthy females. This discrepancy in results may be attributed to the considerably lower increase in plasma Trp–LNAA ratio that was achieved following α-lactalbumin (+80%) relative to the Trp–LNAA ratio achieved with pure Trp (approximately 6-fold increase; Attenburrow et al., 2003). The increase in Trp–LNAA ratio following α-lactalbumin may not have been sufficient to modulate emotional processing (Scrutton et al., 2007).

The available reports suggest that Trp loading in females can induce a positive bias in the processing of emotional stimuli, which is consistent with the effects of serotonergic antidepressants (Harmer et al., 2003, 2004, 2006). There is some indication that these changes occur following higher increases of the Trp–LNAA ratio, but the current dose–response data are very limited. The results also suggest that women may be more susceptible to serotonergic manipulations than men. However, given the small male sample size it is difficult to draw conclusions regarding the effect of Trp loading on emotional processing in men.

3.5. Tryptophan loading and psychomotor performance

Trp loading has consistently been shown to impair motor performance on a range of psychomotor tasks (specifically: Grooved pegboard test, Left/right choice reaction time task, Motor choice reaction time task, and the Symbol copying test), in both healthy adults (Booij et al., 2006; Luciana et al., 2001; Sobczak et al., 2003; Winokur et al., 1986) and in vulnerable populations (Booij et al., 2006; Sobczak et al., 2003) following both Trp loading (range 5–10.3 g) and administration of an α-lactalbumin-rich drink. In line with this, decrements in reaction time performance following Trp loading have also been consistently reported in healthy and sub-group volunteers following both Trp and a carbohydrate rich/protein poor diet (Cunliffe et al., 1998; Markus et al., 1998; Morgan et al., 2007; Murphy et al., 2006). These findings suggest that Trp has a mild sedative effect, which is consistent with previous sleep studies (refer to below Section 5). Although Cunliffe's et al. (1998) findings of a decreased Critical Flicker Fusion threshold (measure of central fatigue) appears to support Trp's sedative effects, the putative effects of pupillary changes were not accounted for. Previous research has shown that modulations to serotonergic activity through administration of SSRIs induce an acute and steady increase in pupil diameter (Schmitt et al., 2002), independently invoking CFF threshold increases. Nevertheless, the observed increase in subjective ratings of fatigue reported by Cunliffe et al. (1998) does lend support for Trp's sedative effects. Furthermore, the fact that decrements to psychomotor and reaction time performance have been reported across different study populations (i.e. healthy, sub-group, clinical populations), further suggests that psychomotor performance impairment may be attributed to the proposed sedative effects of Trp loading, that may be linked to increased melatonin production.

3.6. Conclusion

In summary, the beneficial effects of Trp loading on cognition are generally modest and not always found. Following Trp loading, improvements in long-term memory for verbal and abstract information, as well as memory scanning ability has been shown in vulnerable and clinical populations. In healthy volunteers the results are less consistent. However, Trp loading does appear to induce a positive bias in the processing of emotional stimuli in healthy women, which is consistent with the SSRI literature. Trp loading has also consistently been shown to impair psychomotor and reaction time performance across the different study populations (i.e. healthy adults and vulnerable populations). There is no clear indication that Trp loading affects attention or executive functions, but studies in this field are too limited and heterogeneous to allow any firm conclusions.

4. Effect of tryptophan loading on mood and alertness

Since lowered serotonergic functioning has been implicated in affective disorders (Arango et al., 2002; Deakin, 1998; Delgado, 2000; Mahmood and Silverstone, 2001), the role of 5-HT on mood has been extensively investigated. ATD studies have shown a significant, transient reappearance of depressive symptoms following ATD in both medicated and unmedicated depressed

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patients in remission (Delgado et al., 1990; Smith et al., 1997), and in subjects with family histories of depression (Benkelfat et al., 1994). Although there have been reports of mood-lowering effects of ATD in healthy subjects (Young et al., 1985), the bulk of the literature indicates no effects in healthy volunteers (see Ruhe et al., 2007). Similarly, administration of pro-serotonergic drugs to healthy volunteers generally does not induce mood changes (Merens et al., 2007). Based on these results, it is expected that Trp loading may improve mood in vulnerable populations where dysfunction of the serotonergic system is known. However, in healthy subjects, it is likely that the effects of Trp loading on mood are less clear, with minimal effects expected.

4.1. Effect of tryptophan loading on mood in clinical populations

Over five decades ago Lauer et al. (1958) reported the first observation that Trp loading improves mood. Some of the earlier research investigated the use of Trp with other antidepressant treatments, demonstrating the ability of Trp (doses ranging from 3.5 to 18 g/day) to potentiate the action of monamine oxidase inhibitors and tricyclic antidepressants in depressed patients (Ayuso Gutierre and Lopez-Ibor Alino, 1971; Coppen et al., 1963; Glassman and Platman, 1969; Pare, 1963).

There are a substantial number of studies that have addressed the efficacy of Trp given alone as an antidepressant (Bowers, 1970; Chouinard et al., 1979, 1983; Mendels et al., 1975; Murphy et al., 1974; Steinberg et al., 1999; Thomson et al., 1982), and there are many reviews available on the topic (Baldessarini, 1984; Carroll, 1971; Cole et al., 1980). However, there is little consensus in terms of Trp's efficacy in treating depression as studies vary considerably in terms of sample size, study populations, dosages, study designs, and control conditions. For instance, in severely depressed inpatients, Trp has been shown to have little or no effect when compared with placebo (Chouinard et al., 1983). In contrast, Trp has been reported to be an effective antidepressant in mild to moderately depressed outpatients (Thomson et al., 1982). While in patients with premenstrual dysphoric disorder, Steinberg et al. (1999) found that 6 g L-Trp (given as 2 g three times a day for 17 days) was more effective than placebo in controlling extreme mood swings, dysphoria, irritability, and tension.

4.2. Effect of tryptophan loading on mood and alertness in healthy and vulnerable volunteers

Research investigating the effects of Trp loading on mood in healthy volunteers and in vulnerable subjects with presumed dysfunction of the serotonergic system (i.e. stress-vulnerable subjects, recovered depressed patients, unaffected first-degree relatives of bipolar disorder patients) has also produced varying results. Refer to Table 2 for summary of main findings relating to the effects of Trp loading on mood.

In a recent study in healthy adults, the effects of a hydrolysed protein on plasma Trp–LNAA ratio and mood was compared to other sources of Trp (α-lactalbumin, hydrolysed protein, pure Trp, a Trp-containing synthetic peptide), and a placebo protein (Markus et al., 2008). All of the interventions contained a similar amount of Trp (0.8 g Trp; excluding placebo), but differed in the content of other amino acids. The hydrolysed protein produced significantly faster and greater increases in plasma Trp–LNAA ratio (255%) compared to α-lactalbumin (67%) and pure Trp (191%). Mood (a total mood disturbance score obtained by summing all six factor scores of the POMS questionnaire; the six mood factors include: tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, and confusion-bewilderment) was significantly improved 60 min following the hydrolysed protein and pure Trp. The most profound and durable mood enhancing effects were observed 210 min after intake of the hydrolysed protein. No significant mood effects were observed with α-lactalbumin or the synthetic Trp peptide. The lack of a mood effect in the α-lactalbumin condition is consistent with previous research that has only shown α-lactalbumin to reduce feelings of depression (Markus et al., 1998, 2000) and increase ratings of vigour (Markus et al., 1998) in stress-vulnerable subjects after acute stress exposure (Markus et al., 1998, 2000). These results indicate that larger increases in plasma Trp–LNAA ratio may be more likely to modulate mood, even in healthy adults.

In contrast, Sobczak et al. (2002, 2003) reported increased feelings of anger, depression, fatigue, tension, and decreased feelings of vigour (measured by an abbreviated version of POMS) and alertness (measured by Bond and Lader Visual Analogue Scale) in unaffected first-degree relatives of bipolar disorder patients and healthy controls following a single intravenous 7 g Trp challenge, when compared to placebo. The intervention led to a 1500% increase in plasma Trp–LNAA ratio. This increase in plasma ratio was considerably higher than what was observed by Markus et al. (2008) and this may have resulted in the opposite mood effect, specifically negative effects.

A carbohydrate rich/protein poor drink and an α-lactalbumin-rich drink (chocolate drink containing a whey-protein fraction rich in α-lactalbumin; 2 × 20 g whey-protein containing 12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%) has been shown to reduce feelings of depression (measured by the depression subscale of the Profile of Mood States inventory; Markus et al., 1998, 2000) and increase ratings of vigour (measured by the vigour subscale of the Profile of Mood States [POMS] inventory; Markus et al., 1998) in high stress-vulnerable subjects, exposed to experimental stress, relative to a protein rich/carbohydrate poor drink or a casein diet. In contrast, no effect of Trp loading was observed on measures of mood and depressive symptoms in low stress-vulnerable subjects (control) exposed to experimental stress (Markus et al., 1998, 2000). The effects of the Trp-rich drink on ratings of depression and vigour were found when plasma Trp–LNAA ratio increased by only 48% (Markus et al., 1998, 2000). However, this increase in plasma Trp–LNAA ratio may not have been high enough to modulate mood in healthy adults, based on the findings by Markus et al. (2008) and Sobczak et al. (2002, 2003).

Merens et al. (2005) did not find Trp loading to significantly modulate ratings of depression, anger, fatigue, tension, and vigour (measured with the POMS), in stress-induced unmedicated recovered depressed subjects and healthy controls. Although there was a trend reduction in depressive ratings following α-lactalbumin (2 × 20 g whey-protein fraction rich in α-lactalbumin; containing 12.32 g/kg Trp; Trp/ΣLNAA ratio of 8.7%) in stress-induced unmedicated recovered depressed subjects, a similar decrease was also observed in the casein (placebo) condition. The authors argue that 1-day α-lactalbumin intervention may not be sufficient to prevent a stress-induced deterioration in mood in unmedicated recovered depressed subjects. Furthermore, plasma Trp–LNAA ratio increased by only 21%, which may not have been sufficient to significantly reduce depressive ratings in the recovered depressed subjects.

These findings are consistent with a later study that reported no effects of an α-lactalbumin-rich diet (two drinks containing a whey-protein fraction rich in α-lactalbumin; containing 12.32 g/kg Trp) on POMS subscales (i.e. depression, anger, fatigue, tension, vigour) in recovered unmedicated depressed patients and healthy controls (Booij et al., 2006), when plasma Trp–LNAA ratio increased by 21% from baseline.

Similarly, several other studies that have failed to show modulations to mood following Trp loading in healthy adults also reported relatively small increases in plasma Trp–LNAA ratio (relative to the plasma increases noted by Markus et al. (2008) and

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Sobczak et al. (2002, 2003)). Specifically, Beulens et al. (2004) reported a 16% increase following an α-lactalbumin drink and Scrutton et al. (2007) reported an 80% increase following an α-lactalbumin-rich drink. Murphy et al. (2006) and Luciana et al. (2001) also did not find Trp loading to modulate mood in healthy adults. However, plasma Trp–LNAA ratio was not measured.

In conclusion, the effects of Trp loading on mood factors in healthy volunteers and in vulnerable subjects with presumably sub-optimal central serotonergic function are rather inconsistent, with some reports indicating improvements, other reports showing decreases, yet other studies showing no effect. However, it is plausible that differences in elevations of the plasma Trp–LNAA ratio may elucidate some of these inconsistencies. This will be addressed further in Section 6.

5. Effect of tryptophan loading on sleep

Trp has been shown to have direct effects on the homeostatic regulation of sleep (Minet-Ringuet et al., 2004), by increasing availability of brain 5-HT which has been implicated in the regulation of sleep (Bhatti et al., 1998; Hartmann and Greenwald, 1984). In the pineal gland, 5-HT serves as precursor of melatonin (Kleine and Moore, 1979), a neuro-hormone secreted during the night which acts as the signal for darkness in the internal milieu (Vanecek, 1998).

Nocturnal Trp administration is known to increase physiological concentrations of both serotonin and melatonin (Esteban et al., 2004). Melatonin production in the pineal gland is high during the night and inhibited by light. Therefore, in the evening the synthesis of melatonin is activated and serotonin is converted to melatonin (Richardson, 2005). Administration of Trp during the night can therefore be useful in facilitating sleep as Trp increases the release of melatonin (Hajak et al., 1991).

In addition, 5-HT has some direct effects on sleep. Electrophysiological, neurochemical and neuropharmacological studies have shown serotonergic activation promotes waking and inhibits slow-wave sleep and/or rapid eye movement (REM) sleep. Specifically, serotonergic neurons of the dorsal raphe nucleus fire at a steady rate during waking, but decrease their firing during slow-wave sleep, and almost cease activity during REM sleep (Monti and Jantos, 2008 for review).

The effects of Trp on sleep have been investigated for over four decades, with several older reviews available on this topic (Cole et al., 1980; Hartmann and Greenwald, 1984; Young, 1986). The first study to assess the effects of Trp on sleep, Oswald et al. (1966) reported that 5–10 g Trp decreased the time before onset of REM sleep in healthy adults. Since then much research has been conducted in both healthy and clinical populations, specifically insomniacs, to explore the effects of Trp loading on sleep parameters. Refer to Table 3 for summary of the main findings pertaining to the effects of Trp loading on sleep measures in healthy adults, vulnerable populations, and infants and children.

5.1. Effect of tryptophan loading on sleep parameters in insomniacs

The bulk of evidence indicates that doses as low as 1 g L-Trp significantly reduce sleep latency and increase subjective ratings of sleepiness in subjects with insomnia (Brown et al., 1979; Hartmann et al., 1974; Hartman and Spinweber, 1979; Körner et al., 1986; Spinweber, 1986). Doses below 1 g have shown trends towards decreased sleep latency in mild insomniacs (Hartman and Spinweber, 1979). Although in a recent study Hudson et al. (2005) demonstrated that 250 mg pharmaceutical grade Trp and protein sourced Trp (25 mg deoiled butternut squash seed meal containing 22 mg Trp/1 g protein mixed with 25 mg dextrose) significantly improved subjective and objective sleep measures in clinically diagnosed insomniacs. However, given the small sample size further research is warranted. Overall, these results indicate that Trp at doses as low as 1 g improve time to onset of sleep, and doses below 1 g produce trends in a similar direction.

Few studies have reported modulations to sleep stages in insomniac subjects following Trp loading. Hartman and Spinweber (1979) found Stage IV sleep (deep sleep) to be significantly increased following only 250 mg of L-Trp, with no modulations to sleep observed following 500 mg or 1 g Trp. In a dose–response study, Hartmann et al. (1974) found that 1–15 g of L-Trp decreased sleep latency, but only doses above 5 g increased slow-wave sleep and decreased REM sleep. Other studies have failed to demonstrate modulations to sleep stages (Brown et al., 1979; Spinweber, 1986), which may, in part, be attributed to varying Trp doses. Spinweber (1986) found that 3 g L-Trp did not alter sleep stages or brain electrical activity during sleep in chronic sleep-onset insomniacs. However, significant decreases in sleep latency on nights 4–6 of Trp administration were found relative to placebo. Similarly, Brown et al. (1979) did not report modulations to REM and slow-wave sleep following 1 and 3 g L-Trp compared to placebo in healthy females with mild falling asleep complaints. However, significant reductions in sleep latency following the 3 g Trp dose were observed. In summary, doses at low as 1 g L-Trp significantly reduce sleep latency and doses lower than 5 g do not appear to affect sleep stages.

5.2. Effect of tryptophan loading on sleep parameters in healthy volunteers

In normal subjects, who fall asleep easily, it would be expected that Trp loading would produce minimal hypnotic effects as sleep latency is already short and sleep quality is normal. Nevertheless, sleep parameters have been shown to improve in healthy subjects manifesting no sleep problems. Studies have shown that doses of 500 mg, 1 g (Chauffard-Alboucq et al., 1991), 1.2 g, 2.4 g (George et al., 1989), and 4 g (Spinweber et al., 1983) L-Trp significantly reduced sleep latency and increased subjective ratings of sleepiness in healthy adults during the day (George et al., 1989; Spinweber et al., 1983; Thorleifsdottir et al., 1989) and during the night (Chauffard-Alboucq et al., 1991). Interestingly, significant negative correlations have also been reported between plasma Trp level and sleep latency at 0, 60 and 120 min following 1.2 g and 2.4 g L-Trp administration in healthy adults (George et al., 1989). Similarly, an intravenous challenge of 3 and 5 g L-Trp showed a dose-dependent increase in the percentage of sleep observed during Stages I and II (light sleep) during the day compared to placebo in healthy males (Hajak et al., 1991). During nighttime sleep, sleep latency for Stages I and II and sleep efficiency improved following 1, 3, and 5 g L-Trp compared to placebo. Interestingly, during the nighttime condition plasma melatonin increased considerably higher following 1, 3 and 5 g Trp than during the daytime condition, lending support to the notion that time of day may influence melatonin synthesis (Hajak et al., 1991).

Chauffard-Alboucq et al. (1991) reported an increase in nighttime sleepiness and sedative effects in healthy females following 500 mg and 1 g L-Trp (combined with a carbohydrate load) relative to placebo. This effect was observed when plasma Trp–LNAA ratio increased 200% (500 mg) and 300% (1 g) from baseline, peaking 90 min after Trp administration. Interestingly, peak in perceived sleepiness was also found 90 min following Trp consumption. Although previous studies have reported sleepiness and sedative effects as early as 30 min following Trp administration (Hartmann et al., 1976; Yuwiler et al., 1981), this difference is likely attributed to the significantly higher doses consumed, specifically 4 g (Hartmann et al., 1976) and 50 mg/kg (Yuwiler et al., 1981) Trp.

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Few studies have reported modulations to sleep stages following Trp loading. Furthermore, reports are somewhat inconsistent. Wyatt et al. (1970) found 7.5 g Trp decreased REM sleep and increased non-REM sleep in healthy subjects during the night. Nicholson and Stone (1979) observed an increase in the duration of Stage III (slow-wave sleep) sleep during the day following 4 g L-Trp in healthy males. However, no modulations to sleep stages were reported during nighttime sleep following 2, 4, and 6 g L-Trp. In contrast, Spinweber et al. (1983) did not find 4 g L-Trp to modulate sleep stages during the daytime sleep.

It has been argued that L-Trp may be an effective daytime hypnotic for healthy adults, by facilitating sleep onset at times outside the normal circadian rhythm. Spinweber et al. (1983) found that during waking EEG, 4 g L-Trp significantly increased alpha latency, theta latency, and theta amplitude, and decreased alpha frequency, indicating a reduction in wakefulness. However, no wave bands were modulated during sleep. Similarly, Thorleifsdottir et al. (1989) found that during the day, 2 g Trp increased theta amplitude and decreased alpha amplitude in healthy adults, characterising the EEG of drowsiness. In addition, increased subjective ratings of sleepiness were also reported following morning administration of Trp. Thus, it may be that during the day, during wakefulness, Trp loading has a relaxing and calming effect in healthy adults, whereas it has minimal effects on sleep in healthy adults who fall asleep easily.

5.3. Effect of sub-chronic tryptophan loading on sleep

In patients with severe insomnia, Trp loading seems to either lack the potency that other hypnotic drugs have, or doses have not been high enough to modulate sleep. However, reports indicate that interval and sub-chronic Trp treatment may be an effective approach for improving sleep in severe cases of insomnia.

Several studies have observed improved sleep quality and decreased sleep latencies during and several nights following Trp treatment in chronic insomniacs (Demisch et al., 1987a; Hartman et al., 1983; Schneider-Helmert, 1981). Interestingly, results are consistent across different lengths of treatment period. For example, following three nights of 2 g L-Trp administration, significant improvements to sleep were found to continue during a four night placebo period compared to the pre-Trp baseline (Schneider-Helmert, 1981). Reductions to sleep latency have also been shown 1 week after 1 g L-Trp treatment, but surprisingly not during the 7-day treatment (Hartman et al., 1983). Similarly, improvements in sleep were found following 4 weeks of 2 g L-Trp treatment in patients with chronic insomnia (Demisch et al., 1987a,b). During the control period (4 weeks following the 4 week Trp treatment period), where no Trp was administered, sleep deteriorated in half of the improved patients, i.e. 10 out of 19 subjects (Demisch et al., 1987a).

In healthy adults, five nights of 500 mg Trp administration has also been reported to decrease sleep latency and increase sleep depth, sleepiness, and calming effects, relative to five nights of placebo (Leatherwood and Pollet, 1984). Interestingly, younger females were found to be more sensitive to the sedating effects of Trp than other groups (Leatherwood and Pollet, 1984). These results suggest that in cases of severe insomnia or even in healthy adults, Trp loading may be an effective hypnotic when consumed sub-chronically or intermittently.

5.4. Effect of tryptophan loading on sleep and cognition

A benefit of Trp as a sleep aid is that it does not seem to impair performance the next day following administration as some more potent hypnotics have been shown to do (Johnson and Chernik, 1982; Vermeeren, 2004). In a recent study, the cognitive benefits of evening Trp loading on morning performance were assessed (Markus et al., 2005). As positive associations between Trp availability and sleep have previously been shown (see above), the aim of this study was to ascertain whether evening intake of α-lactalbumin improves morning cognitive performance due to improved sleep. The authors demonstrated that evening consumption of 2 × 20 g α-lactalbumin protein with an enriched Trp content of 4.8 g/100 g Trp, increased plasma Trp availability and the Trp–LNAA ratio by 130%, decreased feelings of sleepiness in the morning, and improved morning alertness and attention (measured by the P300 evoked related potential component) in subjects with and without mild sleep complaints. However, only in subjects with mild sleep complaints did evening consumption of α-lactalbumin improve vigilance performance the following morning. These findings provide support for the notion that Trp loading may improve cognition indirectly by improving sleep.

5.5. Effect of tryptophan loading on sleep in infants and children

The concentration of Trp in human milk varies in relation to the age of the lactating infant, the duration of the milking episode, and the time of day, where it has been shown to be higher during dark time (Cubero et al., 2005). Recently it was shown that oscillations in Trp concentration in maternal milk parallels oscillations in infant urinary 6-sulphatoxy-melatonin (Cubero et al., 2005), thus supporting Trp's important role in maternal milk as a regulator of the circadian rhythms of the infant. However, the internal clock that the oscillating levels of Trp in maternal milk provides, disappears with the use of commercial milk formulas, as the level of Trp found in infant formulas always remains constant (i.e. no difference in Trp level between daytime and nighttime formulas). Furthermore, maternal milk has been shown to contain higher levels of Trp than commercial formulas, which result in formula fed infants manifesting lower plasma Trp concentrations compared to human milk-fed infants (Heine, 1999).

The effect of Trp loading on sleep latency in newborns was first investigated by Yogman and Zeisal (1983). The authors found that newborn infants (2–3 days of age) fed Trp in glucose during an evening feeding manifested shorter sleep latencies, and entered rapid eye movement and quiet sleep (defined as quiescent state with eyes closed, absence of eye movements, little or no motor activity, and slow, regular respiration) sooner than when fed a commercial formula containing Trp. A limitation of this study was that the Trp was ingested in glucose solutions as a single dose, rather than as a constituent of milk which was chronically fed to infants.

Thus, in a later study, Steinberg et al. (1992) investigated whether infant formulas, varying only in Trp content (0, 294, 588 and 882 μmol/L), result in differences to plasma Trp concentration and Trp–LNAA ratio, and whether the Trp–LNAA ratio was predictive of infants' (gestational age of 37–42 weeks) sleep latency. Trp–LNAA ratio, and not plasma Trp concentrations, predicted differences in sleep latency across treatment conditions. Thus, sleep latency was shorter for infants with the highest Trp–LNAA ratios. Infants consuming the high Trp dose (882 μmol/L) manifested shorter sleep latencies than infants consuming human milk. Furthermore, infants receiving the high Trp dose tended to be less alert, spent less time crying, and more time sleeping than the infants fed lower levels of added Trp (0, 294, 588 μmol/L). These findings indicate that infant formula Trp composition can modulate sleep latency and wakefulness in infants.

In a recent study, Aparicio et al. (2007) demonstrated that milk formulas with Trp content that is appropriate to the light–dark variations in Trp level improve the circadian sleep/wake cycles in infants who are not breast fed. Specifically, infants (aged between 12 and 20 weeks) receiving a low Trp formula during the day and a

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high Trp formula during the night, slept more, manifested better sleep efficiency, increased immobility time, had fewer night movements and waking episodes. No difference was found between the two control groups (control group 1: low Trp formula fed throughout the 24 h day; control group 2: low Trp formula fed from 18:00 to 06:00 h and tryptophan-enriched milk (3.4 g Trp/100 g protein) fed from 06:00 to 18:00 h) despite that the Trp content varied considerably (1.5% and 2.72% [note that the latter % is an average value]). These findings indicate that the use of different formulas for day and night feeding constitutes an interesting and novel approach to infant nutrition.

In a large Japanese sample, increased sleep latencies and difficulties waking up in the morning were shown to be associated with lower Trp index scores (Trp content consumed during breakfast) in infants and children (0–8 years; Harada et al., 2007). This effect was not similarly observed in older children (9–15 years). The authors concluded that Trp consumed at breakfast is important to sustain a healthy circadian rhythm and improve quality of sleep. A limitation of this study was that the Trp index was calculated based only on what was consumed at breakfast. Therefore, it cannot be excluded that the observed sleep modulation was due to whole-day or evening dietary Trp intake, of which breakfast measures may be a proxy.

5.6. Conclusion

Most of the beneficial effects of Trp loading on sleep have been shown in subjects with some sleep disturbances, such as patients with mild-moderate insomnia or healthy subjects reporting a longer than average sleep latency. In these subjects, Trp doses as low as 1 g have been shown to improve subjective measures of sleepiness and decrease sleep latency, and doses below 1 g have produced trends in a similar direction. However, modulations to sleep stages have only been observed with doses above 5 g Trp (see Fig. 3).

Interestingly, in healthy subjects who manifest no sleep disturbances, Trp loading has also been shown to increase subjective ratings of sleepiness and reduce sleep latency. Furthermore, Trp appears to be an effective daytime hypnotic for healthy adults, by facilitating sleep onset at times outside the normal circadian rhythm, and modulating sleep stages during the day. Thus, it may be that during wakefulness, Trp loading has a relaxing and calming effect in healthy adults.

In patients with severe sleep insomnia, Trp loading does not appear to be effective as a hypnotic. This may be because Trp lacks the potency that other hypnotic drugs have, or study doses have not been high enough to produce any sleep benefits. However, the literature does suggest that Trp loading may be an effective hypnotic for severe insomniac patients when consumed sub-chronically or intermittently.

In infants, reports indicate that Trp loading improves sleep. Moreover, it seems that varying the Trp content in milk formulas that are appropriate to light–dark variations (i.e. low Trp levels during daytime feeding and high Trp levels during nighttime feeding) improves the sleep/wake cycles of infants who are not breast fed.

6. Discussion

The beneficial effects of Trp loading on cognition are rather modest and not always found. ATD studies have provided the fundamental insights into which cognitive functions are susceptible to modulation of 5-HT and the direction of effects. It would be expected that Trp loading would produce opposite effects to that of ATD. However, this has not generally been the case. Reports vary considerably across the different cognitive domains, study designs, and populations. There are several possible explanations for this.

Given the few Trp loading studies that have been performed, there are considerable differences in methodology, such as, Trp doses, method of administration, treatment regimes, and variances in study populations, which all affect the central 5-HT effects that are achieved, and thus the behavioural outcome of the manipulation.

Variations in Trp dose will inevitably produce different results. However, in addition, variations in Trp found in plasma may also modulate the outcome. As metabolism differs across individuals and populations, the level of plasma Trp would seem to be an important aspect to be taken into consideration. However, only a limited number of studies address this point. It may be that variance in performance is dependent on the level of Trp found in blood rather than as a function of dose administered. Furthermore, plasma Trp–LNAA should also be considered as a means to identify that a specific amount of Trp has been transported to the brain in order to better understand the outcome. This notion is illustrated in Figs. 1 and 2. In healthy subjects, plasma Trp–LNAA increases up to 80% have not been found to modulate mood and memory (with

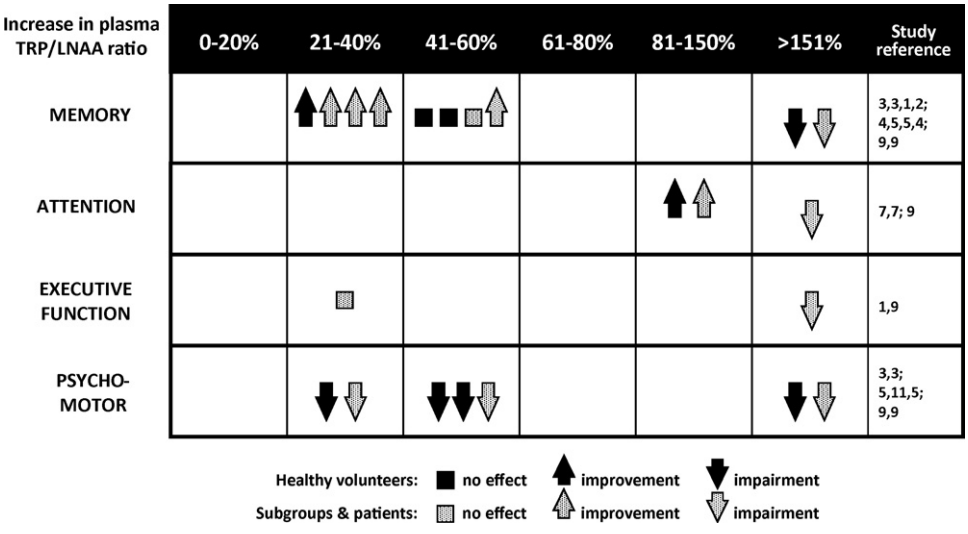

Fig. 1. Summary of the cognitive changes by increase in tryptophan versus large neutral amino acid (TRP–LNAA) ratios after tryptophan loading. Reference numbers are linked to the symbols in order of appearance in the rows and refer to the studies described in Table 1.

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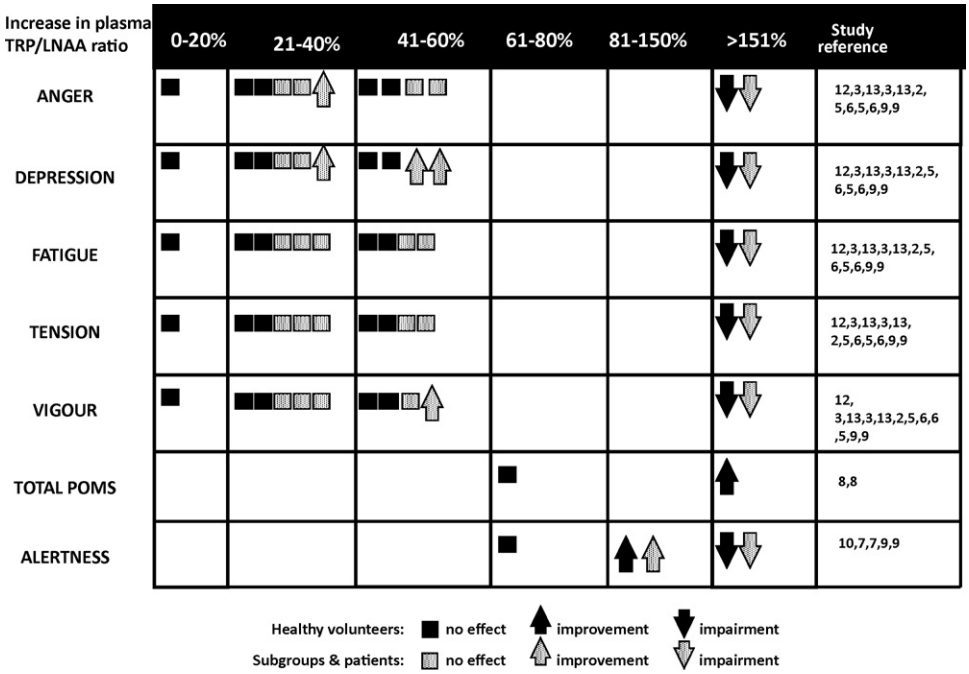

Fig. 2. Summary of the mood changes by increase in tryptophan versus large neutral amino acid (TRP–LNAA) ratios after tryptophan loading. Reference numbers are linked to the symbols in order of appearance in the rows and refer to the studies described in Table 2.

exception of one study). However, larger increases in plasma Trp–LNAA ratio (191–255%) have been shown to improve mood and attention (Markus et al., 2005, 2008). While, considerably large increases in Trp–LNAA ratio (up to 1500%) have been shown to impair memory performance and produce negative mood effects (Luciana et al., 2001; Sobczak et al., 2002, 2003). In vulnerable subjects, it appears that the most beneficial effects of Trp loading on memory, mood and alertness are attained when plasma Trp–LNAA ratio increases 20–60% from baseline. Significant increases in plasma Trp–LNAA ratio (i.e. above 151%) produce negative effects across the different cognitive domains. Note that psychomotor performance has consistently been shown to be impaired across all populations irrespective of the plasma Trp–LNAA ratio. This will be addressed later in the discussion. Future research should report changes in the plasma Trp–LNAA ratio as this may help elucidate the variance in Trp loading effects on cognitive functions in both normal and vulnerable individuals.

The effects of Trp loading may also be dependent on the initial state of the serotonergic system of the subject. Trp loading may either move serotonin towards the optimal level (if the subject has a hypo-serotonergic state to begin with (i.e. depressed, stress-vulnerable, women with premenstrual complaints), thus improving performance, or move serotonin beyond the optimal level if the subject is already at the optimal level to begin with (healthy subjects), thus decreasing performance or producing no effects. Trp loading seems to improve memory performance in vulnerable subjects (i.e. premenstrual symptoms, recovered depressed patients, stress-vulnerable subjects following experimental stress, mild insomniacs), whereas, minimal modulations to memory performance have been shown in healthy subjects. Moreover, based on the ATD and Trp loading literature, it appears to be easier to induce cognitive decrements than to enhance performance in healthy subjects who already have a close to optimal performance level. ATD always move 5-HT activity away from its optimum, thus it is relatively easy to find decrements. However, it seems rather difficult to improve already optimal function. These differences in the initial state of the serotonin system may explain the variance in reported effects, and the lack of mirrored behavioural effects of opposite 5-HT manipulations. Comparing the effects of Trp loading in individuals with low versus normal serotonergic states in the same study could provide a clearer picture as to the influence of initial serotonergic state on the effects of Trp loading. Only few studies have implemented such a design and the general pattern of results is rather inconsistent. Markus et al. (1999, 2002) found improvements in memory scanning ability and mood (Markus et al., 1998, 2000) in high stress-vulnerable individuals with no effects in low stress-vulnerable subjects. In contrast, Booij et al. (2006) reported improvements in abstract visual memory in both vulnerable and control populations. Sobczak et al. (2002, 2003) reported decrements in memory and psychomotor performance and mood in both unaffected first-degree relatives of bipolar disorder patients and healthy controls. Finally, Merens et al. (2005) found no effect on mood in either recovered depressed patients or healthy controls. Taken together, these comparative studies do not indicate that initial state serotonergic function is a strong general determinant of the effects of Trp loading. However, the large heterogeneity in Trp loading methodology and dose, outcome measures and 'vulnerable' study populations hampers a clear cut comparison between studies. Furthermore, the actual presence and extent of a lowered serotonergic state in the investigated populations' remains an assumption as 5-HT activity or vulnerability is not actually measured in the studies.

An important question that therefore needs to be addressed is how we define serotonergic vulnerability. In the scientific literature it generally refers to a vulnerability or sensitivity to natural or experimental modulations or dysregulations to the serotonergic system (Jans et al., 2007). There are a range of factors that can modulate the serotonergic system which subsequently may produce a hypo-serotonergic state. These include innate factors, such as genetics, gender, personality characteristics, prenatal stress; and environmental factors, such as stress and drug use. It has been proposed that the serotonergic functioning of an individual will determine the individual's vulnerability to develop a 5-HT related disorder (Jans et al., 2007). Specifically, the model suggests that as long as the number of innate and environmental factors that disrupt serotonergic functioning are

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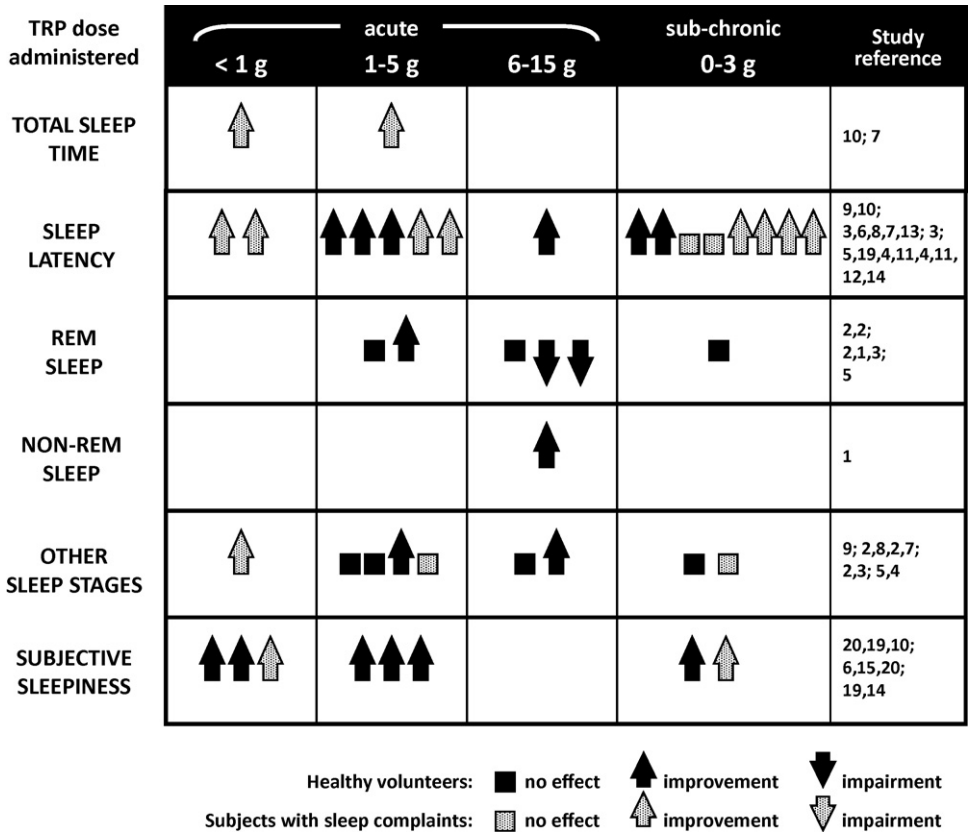

Fig. 3. Summary of the changes in sleep measures by dose of tryptophan administered acutely or sub-chronically. Reference numbers are linked to the symbols in order of appearance in the rows and refer to the studies described in Table 3.

limited, the disturbances they cause to the serotonergic system will be compensated for, and thus no overt behavioural changes should be observed. However, if several of these vulnerability factors occur, a threshold will be reached and the system will no longer be able to compensate (Jans et al., 2007). This is when overt behavioural changes will be observed and pathologies surface. The variance in performance following Trp loading may be related to what is proposed by this model and may also elucidate the lack of any mirror-behavioural effects with ATD reports. It is also important to note that studies implementing manipulations to the serotonergic system establish serotonergic vulnerability only as an outcome, an endpoint. Therefore, there will always be variations in the degree of serotonergic vulnerability within the study population (even if the population is seemingly homogenous i.e. depressed, stress-prone, healthy, etc.), and thus modulations in performance in response to 5-HT challenges will vary across subjects making interpretation of results difficult. Furthermore, differences in the form that serotonergic vulnerability presents itself, for example state or trait, may further complicate interpretation of the effects of various manipulations of the serotonergic system. Specifically, premenstrual syndrome in women or stress may be defined as a state level of serotonergic vulnerability as it is transient. Whereas, depression, a more stable and permanent form of hypo-serotonergic state, can be seen as trait. Thus, manipulations to the serotonergic system (5-HT challenges or ATD) may modulate serotonergic functioning differently for state or trait cases of serotonergic vulnerability, thus producing variance in behavioural outcomes.

It is unclear whether the relationship between serotonergic activity and cognitive function is a linear one or follows an inverted-U curve, where either too little or too much serotonin can impair performance. This may be true irrespective of the initial state of the serotonergic system of the individual. In vulnerable subjects, it seems that Trp loading improves performance when plasma Trp–LNAA ratio increases up to 150% from baseline. However, increases above this have been shown to negatively impact performance across various cognitive domains (Fig. 1). Similarly, in healthy subjects, the effects of Trp loading on memory and mood appear to follow the inverted-U curve hypothesis. Specifically, low doses of Trp attained from α-lactalbumin drinks have been shown to produce minimal effects on memory performance. Similarly, studies that have reported plasma Trp–LNAA increases up to 80%, have not reported mood to be modulated. However, large increases in plasma Trp–LNAA ratio (191–255%) have been shown to improve mood (Markus et al., 2008). Whereas, high doses of Trp (i.e. 7 g IV and 10.3 g) producing increases in Trp–LNAA ratio up to 1500% have been shown to impair memory performance and produce negative mood effects (Luciana et al., 2001; Sobczak et al., 2002, 2003). This could be related to both the initial serotonergic system of the individual (i.e. high serotonin function) or to the Trp dose administered (i.e. high doses). Independent of the positive association of 5-HT activity and function or the inverted-U curve hypothesis, ATD will always move 5-HT activity away from good functioning and thus it is easy to produce decrements. Currently there is insufficient evidence to either support or dismiss an inverted-U curve hypothesis. However, further research investigating this dose–response effect could provide insight into an optimal plasma Trp–LNAA ratio that may improve cognitive performance in healthy adults.

The effects of Trp loading differ across the cognitive domains. Specifically, Trp loading has quite consistently been shown to improve aspects of memory functioning in vulnerable subjects, yet impair motor and reaction time performance within the same population. This does not seem to be attributed to a dose effect as

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the same doses and populations were employed across the cognitive domains. It may be that these cognitive functions are related to different neuroanatomical serotonergic pathways. The hippocampus has long been associated with learning and memory processes (van Strien et al., 2009) and serotonergic projections from the raphe nuclei innervate various hippocampal subregions (King et al., 2008). Long-term memory improvements observed following Trp loading may therefore be linked to increased serotonergic activity in the hippocampus. Animal studies have provided some evidence for memory enhancing effects of augmentation of 5-HT neurotransmission in the hippocampus (e.g. Haider et al., 2006, 2007) although other findings do not support this notion (e.g. Farr et al., 2000; Adams et al., 2008). Delineating the effects of global serotonergic manipulations on the hippocampus is difficult due to the complexity of serotonin receptor sub-types distribution on the different cell types in this region (Meneses, 1999). For example, agonist as well as antagonist 5-HT6 receptors in the hippocampus can improve cognition, and may be related to stimulation or inhibition (via GABAergic interneurons) actions on cholinergic and/or glutaminergic activity, depending on the localisation of the 5-HT6 receptors (King et al., 2008). In humans, decreased activation in the right hippocampus has been observed after ATD, but only during acquisition and not during retrieval of verbal information, and this has been hypothesised to reflect encoding and/or early consolidation deficits (Van der Veen et al., 2006). However, it must be noted that the serotonergic system also innervates other brain areas that are considered to be important for learning and memory, including the medial septum, entorhinal cortex and prefrontal cortext (King et al., 2008) and memory effects of serotonin may therefore result from a complex interplay of 5-HT actions on these as well as other brain areas.

In addition, part of the cognitive effects of Trp loading may be related to non-serotonergic mechanisms, particularly through melatonin. Melatonin production in the pineal gland varies dramatically in a circadian fashion that is internally controlled by the suprachiasmatic nuclei of the anterior hypothalamus with high levels of melatonin being synthesized and secreted during the dark phase and virtually no production during the light phase (Blask, 2009). Melatonin production is also inhibited by exposure to light of sufficient intensity (>200 lux) (Brzezinski, 1997). Nevertheless, Trp loading (3–5 g i.v.) has been shown to markedly and dose dependently increase circulating melatonin in humans during the day, albeit less pronounced as during the night (Hajak et al., 1991). The enterochromaffin cells of the gastrointestinal tract have been proposed as a significant source of circulating melatonin during the day (Bubenik, 2002) and particularly after Trp loading (see Huether, 1994). Interestingly, the melatonin production in the gastrointestinal tract appears to be regulated by food intake rather than photoperiodicity (Bubenik, 2002). Daytime conversion of Trp into melatonin may underlie mild sedating effects of Trp loading, especially at higher dosages, which may be most sensitively detected by psychomotor tasks. Finally, alteration of glutaminergic neurotransmission following Trp loading should be considered as potential mechanism of cognitive effects, as Trp may be metabolised via the kynurenine pathway, yielding quinolinic acid and kynurenic acid that can activate and antagonise the NMDA receptor, respectively (Ruddick et al., 2006).

Few studies have investigated the chronic effects of Trp loading on cognitive functioning in humans. This is an interesting avenue that should be explored further as it can provide insight into the potential long-term benefits of Trp loading. Animal studies have demonstrated that increases in brain 5-HT metabolism following long-term Trp administration enhance memory processes. In addition, human clinical trials assessing the effects of chronic Trp administration in the treatment of depression have demonstrated improvements to mood and a decrease in depressive symptoms. These results suggest that chronic administration of Trp does not necessarily decrease tolerance and desensitise the effects. It may be that Trp loading has more of an accumulative effect, and thus more robust cognitive effects may be seen following chronic administration in healthy adults.

Over the past decades, a role of the central serotonergic system in cognitive functioning has been revealed. In humans, these insights stem largely from experiments describing the consequences of reduced brain serotonergic function, often by means of tryptophan depletion. Now the challenge is to identify under which conditions an augmentation of serotonergic function can exert beneficial effects, particularly in 'healthy' individuals, i.e. without neuropsychiatric diseases, who nevertheless experience sub-optimal mental states (as discussed above). Optimizing mental health through restoration of state or trait serotonergic hypofunction in such individuals is obviously a compelling notion. In non-clinical populations a milder, non-pharmaceutical intervention such as oral Trp loading may be the preferred manner to achieve this. The current data seems to indicate that such an approach may be feasible and valuable, although the research has been rather fragmented and inconsistent in terms of methodologies. A structured approach, including investigations of dose–response relationships, chronic studies and comparative effects in well-characterised (presumably) serotonergically vulnerable populations will not only provide deeper fundamental insights into the role of serotonin in cognition and mood, but will also lead to evidence-based recommendations for the use of Trp to counteract cognitive and affective disturbances, particularly in non-clinical populations.

References

Adams, W., Kusljic, S., van den Buuse, M., 2008. Serotonin depletion in the dorsal and ventral hippocampus: Effects on locomotor hyperactivity, prepulse inhibition and learning and memory. Neuropharmacology 55, 1048–1055.
Ahveninen, J., Kähkönen, S., Pennanen, S., Liesivuori, J., Ilmoniemi, R.J., Jääskeläinen, I.P., 2002. Tryptophan depletion effects on EEG and MEG responses suggest serotonergic modulation of auditory involuntary attention in humans. Neuroimage 16 (4), 1052–1061.
Anderson, I.M., McKie, S., Elliot, R., Williams, S.R., Deakin, J.F.W., 2008. Assessing human 5-HT function in vivo with pharmacoMRI. Neuropharmacology 55, 1029–1037.
Anderson, I.M., Richell, R.A., Bradshaw, C.M., 2003. The effect of acute tryptophan depletion on probalistic choice. Journal of Psychopharmacoloy 17 (1), 3–7.
Aparicio, S., Garau, C., Esteban, S., Nicolau, M.C., Rivero, M., Rial, R.V., 2007. Chrononutrition: use of dissociated day/night infant milk formulas to improve the development of the wake-sleep rhythms. Effects of tryptophan. Nutritional Neuroscience 10 (3/4), 137–143.
Arango, V., Underwood, M.D., Mann, J.J., 2002. Serotonin brain circuits involved in major depression and suicide. Progress in Brain Research 136, 443–453.
Attenburrow, M.J., Williams, C., Odontiadis, J., Reed, A., Powell, J., Cowen, P.J., Harmer, C.J., 2003. Acute administration of nutritionally sourced tryptophan increases fear recognition. Psychopharmacology 169, 104–107.
Ayuso Gutierre, J.L., Lopez-Ibor Alino, J.J., 1971. Tryptophan and an MAOI (nialamide) in the treatment of depression: a double-blind study. International Pharmacopsychiatry 6, 92–97.
Baldessarini, R.J., 1984. Treatment of depression by altering monoamine metabolism: precursors and metabolic inhibitor. Psychopharmacology Bulletin 20, 224–239.
Benkelfat, C., Ellenbogen, M.A., Dean, P., Palmour, R.M., Young, S.N., 1994. Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. Archives of General Psychiatry 51 (9), 687–697.
Beulens, J.W.J., Bindels, J.G., de Graaf, C., Alles, M.S., Wouters-Wesseling, W., 2004. Alpha-lactalbumin combined with a regular diet increases plasma Trp–LNAA ratio. Physiology and Behaviour 81, 585–593.
Bhatti, T., Gillin, J.C., Seifritz, E., Moore, P., Clark, C., Golshan, S., Stahl, S., Rapaport, M., Kelsoe, J., 1998. Effects of a tryptophan-free amino acid drink challenge on normal human sleep electroencephalogram and mood. Biological Psychiatry 43 (1), 52–59.
Blask, D.E., 2009. Melatonin, sleep disturbance and cancer risk. Sleep Medicine Reviews 13, 257–264.
Bowers, M.B., 1970. Cerebrospinal fluid 5-hydroxyindoles and behaviour after L-tryptophan and pyridoxine administration to psychiatric patients. Neuropsychopharmacology 9, 599–604.

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Booij, L., Merens, W., Markus, C.R., Willem Van der Does, A.J., 2006. Diet rich in α-lactalbumin improves memory in unmedicated recovered depressed patients and matched controls. Journal of Psychopharmacology 20 (4), 526–535.
Booij, L., Van der Does, A.J., Haffmans, P.M., Riedel, W.J., Fekkes, D., Blom, M.J., 2005. The effects of high-dose and low-dose tryptophan depletion on mood and cognitive functions of remitted depressed patients. Journal of Psychopharmacology 19 (3), 267–275.
Brown, C.C., Horrom, N.J., Wagman, A.M., 1979. Effects of L-tryptophan on sleep onset insomniacs. Waking Sleeping 3 (2), 101–108.
Brzezinski, A., 1997. Melatonin in humans. The New England Journal of Medicine 336 (3), 186–195.
Bubenik, G.A., 2002. Gastrointestinal melatonin. Digestive Diseases and Sciences 47 (10), 2336–2348.
Carroll, B.J., 1971. Monoamine precursors in the treatment of depression. Clinical Pharmacology and Therapeutics 12, 743–761.
Chan, R.C.K., Shum, D., Toulopoulou, T., Chen, E.Y.H., 2008. Assessment of executive functions: review of instruments and identification of critical issues. Archives of Clinical Neuropsychology 23, 201–216.
Chauffard-Alboucq, F.A., Leathwood, P.D., Dormond, C.A., 1991. Changes in plasma amino acid and subjective sleepiness ratings in humans after consuming L-tryptophan/maltodextrin mixes. Amino Acids 1, 37–45.
Chouinard, G., Young, S.N., Annable, L., Sourkes, T.L., 1979. Tryptophan-nicotinamide, imipramine and their combination in depression: a controlled study. Acta Psychiatrica Scandinavica 59, 395–414.
Chouinard, G., Young, S.N., Bradweijn, J., Annable, L., 1983. Tryptophan in the treatment of depression and mania. In: van Praag, H.M., Mendlewicz, J. (Eds.), Management of Depressions with Monoamine Precursors: Advances in Biological Psychiatry, vol. 10. Karger, Basel, pp. 47–66.
Cole, J.O., Hartmann, E., Brigham, P., 1980. L-Tryptophan: clinical studies. In: Cole, J.O. (Ed.), Psychopharmacology Update. The Collamore Press, Lexington, Massachusetts, pp. 119–148.
Cools, R., Calder, A.J., Lawrence, A.D., Clark, L., Bullmore, E., Robbins, T.W., 2005. Individual differences in threat sensitivity predict serotonergic modulation of amygdala response to fearful faces. Psychopharmacology 180 (4), 670–679.
Coppen, A., Shaw, D.M., Farrell, J.P., 1963. Potentiation of the antidepressant effect of a monoamine-oxidase inhibitor by tryptophan. Lancet 1, 70–81.
Cubero, J., Valero, V., Sánchez, J., Rivero, M., Parvez, H., Rodríguez, A.B., Barriga, C., 2005. The circadian rhythm of tryptophan in breast milk affects the rhythms of 6-sulfatoxymelatonin and sleep in newborn. Neuroendocrinology Letters 26 (6), 657–661.
Cunliffe, A., Obeid, O.A., Powell-Tuck, J., 1998. A placebo controlled investigation of the effects of tryptophan or placebo on subjective and objective measures of fatigue. European Journal of Clinical Nutrition 52, 425–431.
Davis, K.L., Charney, D., Coyle, J.T., Nemerhoff, C. (Eds.), Neuropsychopharmacology: The Fifth Generation of Progress. American College of Neuropsychopharmacology, 2002.
Deakin, J.F., 1998. The role of serotonin in panic, anxiety and depression. International Clinical Psychopharmacology 13 (Suppl. 4), S1–S5.
Delgado, P.L., Charney, D.S., Price, L.H., Aghajanian, G.K., Landis, H., Heninger, G.R., 1990. Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. Archives of General Psychiatry 47, 411–418.
Delgado, P.L., 2000. Depression: the case for a monoamine deficiency. Journal of Clinical Psychiatry 61 (Suppl. 6), 7–11.
Demisch, K., Bauer, J., Georgi, K., Demisch, L., 1987a. Treatment of severe chronic insomnia with L-tryptophan: results of a double-blind cross-over study. Pharmacopsychiatry 20 (6), 242–244.
Demisch, K., Bauer, J., Georgi, K., 1987b. Treatment of severe chronic insomnia with L-tryptophan and varying sleeping times. Pharmacopsychiatry 20 (6), 245–248.
Dougherty, D.M., Marsh, D.M., Mathias, C.W., Dawes, M.A., Bradley, D.M., Morgan, C.J., Badawy, A.A.B., 2007. The effects of alcohol on laboratory-measured impulsivity after L-tryptophan depletion or loading. Psychopharmacology 193 (1), 137–150.
Esteban, S., Nicolaus, C., Garmundi, A., Rial, R.V., Rodríguez, A.B., Ortega, E., Ibars, C.B., 2004. Effect of orally administered L-tryptophan on serotonin, melatonin, and the innate immune response in the rat. Molecular and Cellular Biochemistry 267 (1–2), 39–46.
Evers, E.A.T., Cools, R., Clark, L., Van der Veen, F.M., Jolles, J., Sahakian, B.J., et al., 2005. Serotonergic modulation of prefrontal cortex during negative feedback in probabilistic reversal learning. Neuropsychopharmacology 30 (6), 1–10.
Evers, E.A., Tillie, D.E., Van der Veen, F.M., Lieben, C.K., Jolles, J., Deutz, N.E., et al., 2004. Effects of a novel method of acute tryptophan depletion on plasma tryptophan and cognitive performance in healthy volunteers. Psychopharmacology (Berl) 178 (1), 92–99.
Evers, E.A., Van der Veen, F.M., Fekkes, D., Jolles, J., 2007. Serotonin and cognitive flexibility: neuroimaging studies into the effect of acute tryptophan depletion in healthy volunteers. Current Medical Chemistry 14 (28), 2989–2995.
Farr, S.A., Flood, J.F., Morley, J.E., 2000. The effect of cholinergic, GABAergic, serotonergic, and glutamatergic receptor modulation on posttrial memory processing in the hippocampus. Neurobiology of Learning and Memory 73, 150–167.
Fernstrom, J.D., Wurtman, R.J., 1971. Brain serotonin content: increase following ingestion of carbohydrate diet. Science 174 (13), 1023–1025.
Fernstrom, J.D., Wurtman, R.J., 1972. Brain serotonin content: physiological regulation by plasma neutral amino acids. Science 178 (59), 414–416.
Fone, K.C.F., 2008. An update on the role of the 5-hydroxytryptamine6 receptor in cognitive function. Neuropharmacology 55, 1015–1022.
Fusa-Poli, P., Allen, P., Lee, F., Surguladze, S., Tunstall, N., Fu, C.H., Brammer, M.J., Cleare, A.J., McGuire, P.K., 2007. Modulation of neural response to happy and sad faces by acute tryptophan depletion. Psychopharmacology 193 (1), 31–44.
Fusar-Poli, P., Allen, P., McGuire, P., Placentino, A., Cortesi, M., Perez, J., 2006. Neuroimaging and electrophysiological studies of the effects of acute tryptophan depletion: a systematic review of the literature. Psychopharmacology 188, 131–143.
Gallagher, P., Massey, A.E., Young, A.H., McAllister-Williams, R.H., 2003. Effects of acute tryptophan depletion on executive function in healthy male volunteers. BMC Psychiatry 3, 10.
George, C.F., Millar, T.W., Hanly, P.J., Kryger, M.H., 1989. The effect of L-tryptophan on daytime sleep latency in normals: correlation with blood levels. Sleep 12 (4), 345–353.
Glassman, A.H., Platman, S.R., 1969. Potentiation of a monoamine-oxidase inhibitor by tryptophan. Journal of Psychiatric Research 7, 83–88.
Haider, S., Khaliq, S., Ahmed, S.P., Haleem, D.J., 2006. Long-term tryptophan administration enhances cognitive performance and increases 5HT metabolism in the hippocampus of female rats. Amino Acids 31, 421–425.
Haider, S., Khaliq, S., Haleem, D.J., 2007. Enhanced serotonergic neurotransmission in the hippocampus following tryptophan administration improves learning acquisition and memory consolidation in rats. Pharmacological Reports 59, 53–57.
Hajak, G., Huether, G., Blanke, J., Blomer, M., Freyer, C., Poeggler, B., Reimer, A., Rodenbeck, A., Schulz-Varszegli, M., Ruther, E., 1991. The influence of intravenous L-tryptophan on plasma melatonin and sleep in men. Pharmacology and Psychiatry 24, 17–20.
Halbreich, U., 2003. The aetiology, biology, and evolving pathology of pre-menstrual syndromes. Psychoneuroendocrinology 28 (Suppl. 3), 55–99.
Harada, T., Hirotani, M., Maeda, M., Nomura, H., Takeuchi, H., 2007. Correlation between breakfast tryptophan content and morning–evening in Japanese infants and students aged 0–15 years. Journal of Physiological Anthropology 26 (2), 201–207.
Harmer, C.J., Bhagwager, Z., Perrett, D.I., Völlm, B.A., Cowen, P.J., Goodwin, G.M., 2003. Acute SSRI administration affects the processing of social cues in healthy volunteers. Neuropsychopharmacology 28, 148–152.
Harmer, C.J., Shelley, N.C., Cowen, P.J., Goodwin, G.M., 2004. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. American Journal of Psychiatry 161, 1256–1263.
Harmer, C.J., 2008. Serotonin and emotional processing: does it help explain antidepressant drug action? Neuropharmacology 55, 1023–1028.
Harmer, C.J., Mackay, C.E., Reid, C.B., Cowen, P.J., Goodwin, G.M., 2006. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. Biological Psychiatry 59, 816–820.
Hartmann, E., Cravens, J., List, S., 1974. Hypnotic effects of L-tryptophan. Archives of General Psychiatry 31, 394–397.
Hartmann, E., Spinweber, C.L., Ware, C., 1976. L-Tryptophan, L-leucine, and placebo: Effects on subjective alertness. Sleep Research 5, 57.
Hartmann, E., Greenwald, D., 1984. Tryptophan and human sleep: an analysis of 43 studies. In: Schlossberger, H.G., Kochen, W., Linzen, B., Steinhart, H. (Eds.), Progress in Tryptophan and Serotonin Research. Walter de Gruyter, Berlin, pp. 297–304.
Hartman, E., Lindsley, J.G., Spinweber, C., 1983. Chronic insomnia: effects of tryptophan, flurazepam, secobarbital, and placebo. Psychopharmacology 80 (2), 138–142.
Hartman, E., Spinweber, C.L., 1979. Sleep induced by L-tryptophan. Effect of dosages within the normal dietary intake. The Journal of Nervous and Mental Disease 167 (8), 497–499.
Heine, W.E., 1999. The significance of tryptophan in infant nutrition. Advances in Experimental Medicine and Biology 467, 705–710.
Heine, W., Radke, M., Wutzke, K.D., Peters, E., Kundt, G., 1996. alpha-Lactalbumin-enriched low-protein infant formulas: a comparison to breast milk feeding. Acta Paediatrica 85 (9), 1024–1028.
Hudson, C., Hudson, S.P., Hecht, T., Mackenzie, J., 2005. Protein source tryptophan versus pharmaceutical grade tryptophan as an efficacious treatment for chronic insomnia. Nutritional Neuroscience 8 (2), 121–127.
Huether, G., 1994. Melatonin synthesis in the gastrointestinal tract and the impact of nutritional factors on circulating melatonin. Annals of the New York Academy of Sciences 31, 146–158.
Hughes, J.H., Gallagher, P., Stewart, M.E., Matthews, D., Kelly, T.P., Young, A.H., 2003. The effects of acute tryptophan depletion on neuropsychological function. Journal of Psychopharmacology 17, 300–319.
Jacob, B.L., Fornal, C.A., 1995. Serotonin and behaviour. A general hypothesis. In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. Raven Press Ltd., New York, pp. 461–469.
Jans, L.A.W., Riedel, W.J., Markus, C.R., Blokland, A., 2007. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. Molecular Psychiatry 12, 522–543.
Johnson, L.C., Chernik, D.A., 1982. Sedative-hypnotics and human performance. Psychopharmacology (Berl) 76 (2), 101–113.
Joseph, M.H., Kennett, G.A., 1983. Stress-induced release of 5-HT in the hippocampus and its dependence on increased tryptophan availability: an in vivo electrochemical study. Brain Research 270, 251–257.
Khaliq, S., Haider, S., Ahmed, S.P., Perveen, T., Haleem, D.J., 2006. Relationship of brain tryptophan and serotonin in improving cognitive performance in rats. Pakistani Journal of Pharmaceutical Sciences 19 (1), 11–15.

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King, M.V., Marsden, C.A., Fone, K.C.F., 2008. A role for the 5-HT1A, 5-HT4 and 5-HT6 receptors in learning and memory. Trends in Pharmacological Sciences 29 (9), 482–492.

Kleine, D.C., Moore, R.Y., 1979. Pineal N-acetyltransferase and hydroxyindole-O-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. Brain Research 174 (2), 245–262.

Körner, E., Bertha, G., Flooh, E., Reinhart, B., Wolf, R., Lechner, H., 1986. Sleep-inducing effect of L-tryptophane. European Neurology 25 (2), 75–81.

Kouri, E.M., Halbreich, U., 1997. State and trait serotonergic abnormalities in women with dysphoric premenstrual syndromes. Psychopharmacological Bulletin 33, 767–770.

Lauer, J.W., Inskip, W.M., Bernsohn, J., Zeller, E.A., 1958. Observations on schizophrenic patients after iproniazid and tryptophan. Archives of Neurology and Psychiatry 80, 122–130.

Leatherwood, P.D., Pollet, P., 1984. Tryptophan (500 mg) decreases subjectively perceived sleep latency and increases sleep depth in man. In: Schlossberger, H.G., et al. (Eds.), Progress in Tryptophan and Serotonin Research. Berlin de Gruyter, pp. 311–314.

LeMarquand, D.G., Pihl, R.O., Young, S.N., Tremblay, R.E., Seguin, J.R., Palmour, R.M., Benkelfat, C., 1998. Tryptophan depletion, executive functions, and disinhibition in aggressive, adolescent males. Neuropsychopharmacology 19 (4), 333–341.

Luciana, M., Burgund, E.D., Berman, M., Hanson, K.L., 2001. Effects of tryptophan loading on verbal, spatial and affective working memory functions in healthy adults. Journal of Psychopharmacology 15, 219–230.

Mahmood, T., Silverstone, T., 2001. Serotonin and bipolar disorder. Journal of Affective Disorders 66 (1), 1–11.

Markus, C.R., Firk, C., Gerhardt, C., Kloek, J., Smolders, G.F., 2008. Effect of different tryptophan sources on amino acids availability to the brain and mood in healthy volunteers. Psychopharmacology (Berl.) 201 (1), 107–114.

Markus, C.R., Jonkman, L.M., Lammers, J., Deutz, N., Messer, M.H., Rigtering, N., 2005. Evening intake of α-lactalbumin increases plasma tryptophan availability and improves morning alertness and brain measures of attention. The American Journal of Clinical Nutrition 81, 1026–1033.

Markus, C.R., Olivier, B., de Haan, E., 2002. Whey protein rich in α-lactalbumin increases the ratio of plasma tryptophan to the sum of the other large neutral amino acids and improves cognitive performance in stress-vulnerable subjects. The American Journal of Clinical Nutrition 75, 1051–1056.

Markus, C.R., Olivier, B., Panhuysen, G.E.M., Van der Gugten, J., Alles, M.S., Tuiten, A., Westenburg, H.G.M., Fekkes, D., Koppeschaar, H.F., de Haan, E., 2000. The bovine protein α-lactalbumin increase the plasma ratio of tryptophan to the other large amino acids, and in vulnerable subjects raises brain serotonin activity, reduces cortisol concentration, and improves mood under stress. The American Journal of Clinical Nutrition 71, 1536–1544.

Markus, C.R., Panhuysen, G., Tuiten, A., Koppeschaar, H., Fekkes, D., Peters, M.L., 1998. Does carbohydrate-rich, protein-poor food prevent a deterioration of mood and cognitive performance of stress-prone subjects when subjected to a stressful Task? Appetite 31, 49–65.

Markus, C.R., Panhuysen, G., Jonkman, L.M., Bachman, M., 1999. Carbohydrate intake improves cognitive performance of stress-prone individuals under controllable laboratory stress. British Journal of Nutrition 82, 457–467.

Marsh, D.M., Dougherty, D.M., Moeller, F.G., Swann, A.C., Spiga, R., 2002. Laboratory-measured aggressive behaviour of women: acute tryptophan depletion and augmentation. Neuropsychopharmacology 26 (5), 660–671.

Mendels, J., Stinnett, J.L., Burns, D., Frazer, A., 1975. Amine precursors and depression. Archives of General Psychiatry 32, 22–30.

Mendelsohn, D., Riedel, W.J., Sambeth, A., 2009. Effects of acute tryptophan depletion on memory, attention and executive functions: a systematic review. Neuroscience and Biobehavioural Reviews 33 (6), 926–952.

Meneses, A., 1999. 5-HT system and cognition. Neuroscience and Biobehavioural Reviews 23 (8), 1111–1125.

Meneses, A., 2007a. Stimulation of 5-HT1A, 5-HT1B, 5-HT2A/2C, 5-HT3 and 5-HT4 receptors or 5-HT uptake inhibition: short-and long-term memory. Behavioural Brain Research 184, 81–90.

Meneses, A., Perez-Garcia, G., 2007b. 5-HT1A and memory. Neuroscience and Biobehavioural Reviews 31 (5), 705–727.

Merens, W., Booij, L., Markus, R., Zitman, F.G., Onkenhout, W., Willem Van der Does, A.J., 2005. The effects of a diet enriched with α-lactalbumin on mood and cortisol response in unmedicated recovered depressed subjects and controls. British Journal of Nutrition 94, 415–422.

Merens, W., Van der Does, A.J.W., Spinhoven, P., 2007. The effects of serotonin manipulations on emotional information processing and mood. Journal of Affective Disorders 103, 43–62.

Minet-Ringuet, J., Le Ruyet, P.M., Tomé, D., Even, P.C., 2004. A tryptophan-rich protein diet efficiently restores sleep after food deprivation in the rat. Behavioural Brain Research 152 (2), 335–340.

Monleon, S., Vinader-Caerols, C., Arenas, M.C., Parra, A., 2008. Antidepressant drugs and memory: insights from animal studies. European Neuropsychopharmacology 18, 235–248.

Monti, J.M., Jantos, H., 2008. The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking. Progress in Brain Research 172, 625–646.

Morgan, R.M., Parry, A.M.M., Arida, R.M., Matthews, P.M., Davies, B., Castell, L.M., 2007. Effects of elevated plasma tryptophan on brain activation associated with the stroop task. Psychopharmacology 190, 383–389.

Murphy, D.L., Baker, M., Goodwin, F.K., Miller, L., Kotin, J., Bunney, W.E., 1974. L-Tryptophan in affective disorders: indoleamine changes and differential clinical effects. Psychopharmacology 34, 11–20.

Murphy, S.E., Longhitano, C., Ayres, R.E., Cowen, P.J., Harmer, C., 2006. Tryptophan supplementation induces a positive bias in the processing of emotional material in healthy female volunteers. Psychopharmacology 187, 121–130.

Murphy, F.C., Smith, K.A., Cowen, P.J., Robbins, T.W., Sahakian, B.J., 2002. The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. Psychopharmacology 163 (1), 42–53.

Nicholson, A.N., Stone, B.M., 1979. L-Tryptophan and sleep in healthy man. Electroencephalogram and Clinical Neurophysiology 47 (5), 539–545.

Nishizawa, S., Benkelfat, C., Young, S.N., Leyton, M., Mzengeza, S., de Montigny, C., Blier, P., Diksic, M., 1997. Differences between males and females in rates of serotonin synthesis in human brain. Proceedings of the National Academy of Sciences of the United States of America 94 (10), 5308–5313.

Oswald, I., Ashcroft, G.W., Berger, R.J., Eccleston, D., Evans, J.I., Thacore, V.R., 1966. Some experiments in the chemistry of normal sleep. British Journal of Psychiatry 112, 391–399.

Pare, C.M.B., 1963. Potentiation of monoamine-oxidase inhibitors by tryptophan. Lancet ii, 527–528.

Park, S.B., Coull, J.T., McShane, R.H., Young, A.H., Sahakian, B.J., Robbins, T.W., Cowen, P.J., 1994. Tryptophan depletion in normal volunteers produces selective impairments in learning and memory. Neuropharmacology 33 (3–4), 575–588.

Rabbitt, P., 1997. Introduction: methodologies and models in the study of executive function. In: Rabbitt, P. (Ed.), Methodology of Frontal and Executive Function. Psychology Press Ltd., East Sussex, UK, pp. 1–38.

Richardson, G.S., 2005. The human circadian system in normal and disordered sleep. Journal of Clinical Psychiatry 66 (Suppl 9), 3–9.

Riedel, W.J., Klaassen, T., Deutz, N.E., van Someren, A., van Praag, H.M., 1999. Tryptophan depletion in normal volunteers produces selective impairment in memory consolidation. Psychopharmacology (Berl) 141 (4), 362–369.

Riedel, W.J., Eikmans, K., Heldens, A., Schmitt, J.A., 2005. Specific serotonergic reuptake inhibition impairs vigilance performance acutely and after subchronic treatment. Journal of Psychopharmacology 19, 12–20.

Rogers, R.D., Everitt, B.J., Baldacchino, A., Blackshaw, A.J., Swainson, R., Wynne, K., Baker, N.B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J.F., Sahakian, B.J., Robbins, T.W., 1999. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology 20 (4), 322–339.

Rogers, R.D., Tunbridge, E.M., Bhagwagar, Z., Drevets, W.C., Sahakian, B.J., Carter, C.S., 2003. Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. Neuropsychopharmacology 28, 153–162.

Roiser, J.P., Muller, U., Clarke, L., Sahakian, B.J., 2007. The effects of acute tryptophan depletion and serotonin transporter polymorphism on emotional processing in memory and attention. International Journal of Neuropsychopharmacology 10 (4), 449–461.

Roiser, J.P., Levy, J., Fromm, S.J., Wang, H., Hasler, G., Sahakian, B.J., Drevets, W.C., 2008. The effect of acute tryptophan depletion on the neural correlates of emotional processing in healthy volunteers. Neuropsychopharmacology 33 (8), 1992–2006.

Rowley, B., Van, F., Mortimore, C., Connell, J., 1998. Effects of acute tryptophan depletion on tests of frontal and temporal lobe function. Journal of Psychopharmacology 12, A60.

Ruddick, J.P., Evans, A.K., Nutt, D.J., Lightman, S.L., Rook, G.A.W., Lowry, C.A., 2006. Tryptophan metabolism in the central nervous system: medical implications. Expert Reviews in Molecular Medicine 8 (20), 1–27.

Ruhe, H.G., Mason, N.S., Schene, A.H., 2007. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Molecular Psychiatry 12 (4), 331–359.

Sambeth, A., Blokland, A., Harmer, C.J., Kilkens, T.O.C., Nathan, P.J., Porter, R.J., Schmitt, J.A.J., Scholtissen, B., Sobczak, S., Young, A.H., Riedel, W.J., 2007. Sex differences in the effect of acute tryptophan depletion on declarative episodic memory: a pooled analysis of nine studies. Neuroscience and Biobehavioural Reviews 31, 516–529.

Sayegh, R., Schiff, I., Wurtman, J., Spiers, P., McDermott, J., Wurtman, R., 1995. The effect of a carbohydrate-rich beverage on mood, appetite, and cognitive function in women with premenstrual syndrome. Obstetrics and Genecology 86 (4), 520–528.

Schmitt, J.A., Jorissen, B.L., Sobczak, S., van Boxtel, M.P., Hogervorst, E., Deutz, N.E., Riedel, W.J., 2000. Tryptophan depletion impairs memory consolidation but improves focussed attention in healthy young volunteers. Journal of Psychopharmacology 14 (1), 21–29.

Schmitt, J.A., Jorissen, B.L., Dye, L., Markus, C.R., Deutz, N.E., Riedel, W.J., 2005. Memory function in women with premenstrual complaints and the effect of serotonergic stimulation by acute administration of an alpha-lactalbumin protein. Journal of Psychopharmacology 19 (4), 375–384.

Schmitt, J.A.J., Ramaekers, J.G., Kruizinga, M., Van Boxtel, M.P.J., Vuurman, E.F.P.M., Riedel, W.J., 2002. Additional dopamine reuptake inhibition attenuates vigilance decrement induced by serotonergic reuptake inhibition in man. Journal of Psychopharmacology 16, 207–214.

Schmitt, J.A.J., Wingen, M., Ramaekers, J.G., Evers, E.A.T., Riedel, W.J., 2006. Serotonin and human cognitive performance. Current Pharmaceutical Design 12, 2473–2486.

Schneider-Helmert, D., 1981. Interval therapy with L-tryptophan in severe chronic insomniacs. A predictive laboratory study. International Pharmacopsychiatry 16 (3), 162–173.

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Scrutton, H., Carbonnier, A., Cowen, P.J., Harmer, C.J., 2007. Effects of α-lactalbumin on emotional processing in healthy women. Journal of Psychopharmacology 21 (5), 519–524.
Smith, K.A., Fairburn, C.G., Cowen, P.J., 1997. Relapse of depression after rapid depletion of tryptophan. Lancet 349, 915–919.
Sobczak, S., Honig, A., van Duinen, M.A., Maes, M., Riedel, W.J., 2002. Mood, prolactin and cortisol responses following intravenous L-tryptophan challenge: evidence for serotonergic vulnerability in first-degree relatives of bipolar patients. International Journal of Neuropsychopharmacology 5, 249–254.
Sobczak, S., Honig, A., Schmitt, J.A.J., Riedel, W.J., 2003. Pronounced cognitive deficits following an intravenous L-tryptophan challenge in first-degree relatives of bipolar patients compared to healthy controls. Neuropsychopharmacology 28, 711–719.
Spinweber, C.L., 1986. L-tryptophan administered to chronic sleep-onset insomniacs: late-appearing reduction of sleep latency. Psychopharmacology 90 (2), 151–155.
Spinweber, C.L., Ursin, R., Hilbert, R.P., Hilderbrand, R.L., 1983. L-Tryptophan: effects on daytime sleep latency and the waking EEG. Electroencephalogram and Clinical Neurophysiology 55 (6), 652–661.
Stanford, S.C., 1993. Monoamines in response and adaptation to stress. In: Stanford, S.C., Salmon, P. (Eds.), Stress, From Synapse to Syndrome. Academic Press, London, pp. 24–30.
Steinberg, S., Annable, L., Young, S.N., Liyanage, N., 1999. A placebo-controlled clinical trial of L-tryptophan in premenstrual dysphoria. Biological Psychiatry 45, 313–320.
Steinberg, L.A., O'Connell, N.C., Hatch, T.F., Picciano, M.F., Birch, L.L., 1992. Tryptophan intake influences infants sleep latency. The Journal of Nutrition 122 (9), 1781–1791.
Talbot, P.S., Watson, D.R., Barrett, S.L., Cooper, S.J., 2006. Rapid tryptophan depletion improves decision-making cognition in healthy humans without affecting reversal learning or set shifting. Neuropsychopharmacology 31 (7), 1519–1525.
Thomson, J., Rankin, H., Ashcroft, G.W., Yates, C.M., McQueen, J.K., Cummings, S.W., 1982. The treatment of depression in general practice: a comparison of L-tryptophan, amitriptyline, and a combination of L-tryptophan and amitriptyline with placebo. Psychological Medicine 12, 741–751.
Thorleifsdottir, B., Björnsson, J.K., Kjeld, M., Kristbjarnarson, H., 1989. Effects of L-tryptophan on daytime arousal. Neuropsychobiology 21 (3), 170–176.
Van der Veen, F.M., Evers, E.A.T., van Deursen, J.A., Deutz, N.E.P., Backes, W.H., Schmitt, J.A.J., 2006. Acute tryptophan depletion reduces activation in the right hippocampus during encoding in an episodic memory task. NeuroImage 31, 1188–1196.
Van der Veen, F.M., Evers, E.A., Deutz, N.E., Schmitt, J.A., 2007. Effects of acute tryptophan depletion on mood and facial emotion perception related brain activation and performance in healthy women with and without family history of depression. Neuropsychopharmacology 32 (1), 216–224.
van Strien, N.M., Cappaert, N.L.M., Witter, M.P., 2009. The anatomy of memory: an interactive overview of the parahippocampal–hippocampal network. Nature Reviews: Neuroscience 10, 272–282.
Vanecek, J., 1998. Cellular mechanisms of melatonin action. Physiological Reviews 78 (3), 687–721.
Vermeeren, A., 2004. Residual effects of hypnotics: epidemiology and clinical implications. CNS Drugs 18 (5), 297–328.
Wingen, M., Kuypers, K.P., van de Ven, V., Formisano, E., Ramaekers, J.G., 2008. Sustained attention and serotonin: a pharmaco-fMRI study. Human Psychopharmacology 23 (3), 221–230.
Winokur, A., Lindberg, N.D., Lucki, I., Phillips, J., Amsterdam, J.D., 1986. Hormonal and behavioral effects associated with intravenous L-tryptophan administration. Psychopharmacology (Berl) 88 (2), 213–219.
Wyatt, R.J., Engelman, K., Kupfer, D.J., Fram, D.H., Sjoerdsma, A., Snyder, F., 1970. Effects of L-tryptophan (a natural sedative) on human sleep. Lancet ii, 842–846.
Yogman, M.W., Zeisal, S.H., 1983. Diet and sleep patterns in newborn infants. The New England Journal of Medicine 309 (19), 1147–1149.
Young, S.N., 1986. The clinical psychopharmacology of tryptophan. Nutrition and the Brain 7, 49–88.
Young, S.N., 1996. Behavioural effects of dietary neurotransmitter precursors: basic and clinical aspects. Neuroscience and Biobehavioural Reviews 20 (2), 313–323.
Young, S.N., Gauthier, S., 1981. Tryptophan availability and the control of 5-hydroxytryptamine and tryptamine synthesis in human CNS. Advances in Experimental Medicine and Biology 133, 221–230.
Young, S.N., Smith, S., Pihl, R.O., Ervin, F.R., 1985. Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology 87 (2), 173–177.
Yuwiler, A., Brammer, G.L., Morley, J.E., 1981. Short-term and repetitive administration of oral tryptophan in normal men. Archives of General Psychiatry 38, 619–626.

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