Brain monoamines and early visual information-processing speed

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Abstract

Visual inspection time (IT) is a measure of information-processing speed, which correlates reliably with psychometric intelligence. Pharmacological research into IT indicates that manipulation of the cholinergic system modulates performance on the IT task, however the contribution of other neurotransmitters to this modality remains unclear. This study was designed to examine the effects of low brain serotonin and catecholamine availability on IT using the established method of amino-acid precursor depletion. Female participants (n = 13) completed three experimental sessions; tryptophan depletion (TD); tyrosine/phenylalanine depletion (TPD); and a balanced control condition (B) in a randomized, double-blind crossover design. IT assessments were performed at baseline and approx. 5 h post-mixture administration. IT scores were unaffected by either of the treatment conditions. These findings suggest that monoamines, whilst implicated in various forms of cognition are not central to IT, which measures the efficiency of perceptual intake and information-processing speed.

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Introduction

Inspection time (IT) is a psychophysical rating of information-processing speed that correlates with performance on standardized intelligence tests (Grudnik and Kranzler, 2001; Nettelbeck, 1987). Essentially IT is a backward-masking task, which can be defined as the minimum time (ms) an individual requires to maintain accuracy (e.g. 80%) on a simple two-choice discrimination challenge (Nettelbeck and Lally, 1976). Unlike other elemental cognitive tasks that have been used to examine the relationship between ‘speed of processing’ factors (e.g. reaction time) and higher cognition, IT scores are not confounded by differences in motor response, strategy use or motivation (Deary and Stough, 1996).

In recent times there has been interest in studies that attempt to translate IT performance and the variance it shares with IQ scores to underpinning biological processes (Deary et al., 2001; Stough et al., 2001). Clinical evidence has suggested that patients with Alzheimer’s disease (AD) have significantly impaired ITs compared to age- and IQ-matched controls and patients with Korsakoff’s dementia (Deary et al., 1991). This finding provided the first link between IT and a putative neurochemical substrate, namely, the cholinergic system. Follow-up studies in our laboratory have since reported that cholinomimetics and cholinergic receptor antagonists modulate IT performance. Specifically, compounds that increase ACh release, such as nicotine and donepezil improved IT, while drugs that inhibit ACh release such as mecamylamine impair IT (Hutchinson et al., 2001; Stough et al., 1995; Thompson et al., 2000, 2002). These results have been interpreted as supporting a cholinergic basis to IT (Nathan and Stough, 2001), and are in line with the hypothesized role for cholinergic neurons in gating cortico-sensory information flow (Calaway et al., 1992; Sarter and Bruno, 1999).

Cognitive slowing, as evident on backward-masking tasks and various other information-processing correlates, has been reported in many clinical states such as schizophrenia and depression where abnormalities in multiple neurochemical systems are implicated. Recently, Tsourtos et al. (2002) reported that speed...
of information processing, as measured by IT, was impaired in young, unmedicated unipolar depressed patients when compared to medicated patients that were matched for age, sex and IQ. This latter finding suggests that the slowing of ITs in depression may be ameliorated by antidepressant medication, which pharmacologically implies changes in the activity of other neurotransmitters such as serotonin and the brain catecholamines, dopamine and noradrenaline. Considering that IT has been shown to account for considerable variance (25%) of standardized intelligence scores (Grudnik and Kranzler, 2001), demonstrating that other neurotransmitters play a role in modulating this function may have implications for restoring aspects of cognitive/intellectual impairment in psychiatric disorders.

This preliminary investigation was designed to assess the effects of monoamine availability on early information-processing speed using the IT task. We chose the established method of tryptophan (Trp) depletion (TD) to lower serotonin metabolism and release in normal controls (for methodological review see Moore et al., 2000). TD was compared to the analogous method of tyrosine (Tyr) and phenylalanine (Phe) depletion (TPD), which has been developed as an experimental probe for the catecholamine system (McTavish et al., 1999).

Methods

Subjects

Thirteen female volunteers, aged 20–35 (mean ± S.E.M.; 21.92 ± 1.14 yr) completed the entire study sequence. Subjects were included if they were non-smokers, and were not taking any prescription medication (other than oral contraceptives, n = 10). All participants were screened for medical and psychiatric suitability during a semi-structured assessment with a clinician. To enhance the power of this preliminary study only female subjects were recruited based on evidence that TD reduces brain serotonin synthesis and release more in females than in males (Nishizawa et al., 1997).

Design

The study was conducted in a double blind, placebo-controlled, three-way cross-over design. All participants attended three full-day testing sessions, separated by a minimum 5-d washout period (mean ± S.E.M.; 9.30 ± 1.07 d). Individual assignment to the order of treatment was randomized with each participant completing the three treatment conditions; (1) a 16-part amino-acid control mixture (B); (2) an equivalent mixture deficient in Trp (TD); (3) an equivalent mixture deficient in Tyr and Phe (TPD).

Amino-acid suspension

The composition of the amino-acid mixtures was based on the original 100 g balanced (B) suspension developed by Young et al. (1985), which has been modified to 86 g to account for the lower body weight of women (g): L-alanine, 4.58; L-arginine 4.08; L-cysteine 2.25; glycine 2.97; L-histidine, 2.67; L-isoleucine, 6.67; L-leucine, 11.25; L-lysine monohydrochloride, 9.17; L-methionine, 2.50; L-proline, 10.17; L-serine, 5.75; L-threonine, 5.42; L-valine, 7.42; L-tryptophan, 1.92; L-tyrosine, 5.75; L-phenylalanine, 4.75. Drinks were prepared within a few minutes of oral administration by mixing the powdered amino acids with 180 ml of orange juice. Due to the unpleasant taste of L-cysteine, L-methionine and L-arginine these were administered separately in gelatin capsules.

Procedures

Before each testing session, participants were instructed to follow a structured dietary plan of appropriate low-protein foods (total content <20 g) (Young et al., 1985). On each testing day, subjects arrived at the hospital between 08:30 and 09:00 hours having fasted from 19:00 hours the previous evening. Prior to the mixture administration, baseline IT testing and blood sampling was performed. At 5 h post-ingestion, IT testing and blood sampling was undertaken for a second time.

At 1 and 3 h after drink administration a side-effect checklist was administered. The checklist contained the following items: headache, feeling cold, feeling hot, dizziness, perspiration, blurred vision, nausea, palpitations, dry mouth and abdominal complaints which were summed into a total side-effects score. After 21/2 h, subjects were given a low-protein snack to minimize any hunger discomfort, and upon conclusion of each testing session high protein foods were given to replete their amino-acid balance. All subjects resumed a normal diet between experimental sessions. This study gained ethical approval from the hospital and university research ethics committees. All participants gave written informed consent to take part in this study.

Inspection time (IT) procedure

IT is used to measure the speed of intake of information and discriminative judgement ability (Deary and Stough, 1996). The task procedure was identical to that employed in prior studies relating drug-induced changes to IT performance. Subjects were informed that
the task involved a simple visual discrimination challenge in which they were required to judge the shorter of two lines presented on a computer monitor. The task instructions emphasized accurate responding and that speed of response was not being assessed. To measure IT, a small central circular cue appeared prior to the target stimulus for 500 ms. The target stimulus was comprised of two vertical lines, one 29 mm in length, the other 21 mm that were presented at durations ranging from 16 to 192 ms. The stimulus lines were positioned 16 mm apart and connected at the top by a horizontal line (see Figure 1). A backward mask followed each stimulus presentation for 500 ms to prevent iconic sampling. The pattern mask (‘flash’) consisted of a pair of equal length bolded lines that covered the stimulus area.

Participants were seated approx. 0.5 m from the computer monitor with the keyboard placed comfortably in front of them, and were requested to sit upright throughout the task. Responses were made with the left index finger on the ‘Z’ key and the right index finger on the ‘?’ key. Following each stimulus-mask presentation, participants were instructed to indicate the shorter of the two stimulus lines, i.e. left or right, which varied with equal probability. Each inter-trial interval was 2 s, commencing only after the subject had responded. Parameter estimation by sequential testing procedure (PEST; Taylor and Creelman, 1967) was employed to vary the stimulus duration across trials until a stimulus presentation time (e.g. 45 ms) was reached and remained stable at the programmed accuracy level of 80%. The stimulus duration that was required for this level of accuracy was recorded as the subject’s IT. Five practice recordings were conducted at stimulus times of 300, 200, 160, 100 and 80 ms, programmed with 10 trials each.

**Biochemical and statistical analysis**

Plasma was separated by centrifugation, harvested and stored at –20 °C until quantitative amino-acid analysis. Free plasma Trp (non-albumin bound), plasma Tyr and Phe concentrations were quantified using high-performance liquid chromatography (HPLC) with fluorometric detection as described by Young et al. (1985).

Data were analysed by using repeated-measure ANOVAs (condition × time). When interactions were significant, planned trend-analyses were performed. Post-hoc calculations showed a power of 65% for the IT task with an effect size explaining less than 20% of the variance in scores.

**Results**

Following the balanced mixture (B), there was a significant interaction of condition on plasma-free Trp, Tyr and Phe levels [F(2,18) = 11.74, p < 0.001]. Post-hoc tests showed that all amino-acid concentrations increased from baseline to 5 h (see Table 1). Following the TD mixture, there was a significant interaction between condition and time [F(2,16) = 22.56, p < 0.0001]. Plasma-free concentrations of Trp dropped significantly from baseline values to 5 h (96.52%), compared to increases in Tyr and Phe. Following the TPD mixture, there was a significant interaction between conditions and time [F(2,18) = 15.84, p < 0.0001]. Plasma Tyr (63.85%) and Phe (78.67%) concentrations dropped significantly from baseline to 5 h, compared to increased Trp (142.22%).

No interaction between condition and time for IT scores (ms) were observed [F(2,24) = 0.733, p = 0.491], nor were there significant differences in total trials needed to reach the predetermined 80% accuracy threshold [F(2,24) = 0.127, p = 0.881]. Summary statistics for IT scores are presented in Table 2.

Data was analysed for subjects who completed the entire study schedule (n = 13). No adverse effect to the amino-acid conditions were observed on subjective ratings of vegetative symptoms [F(2,24) = 1.66, p = 0.221].

**Discussion**

While monoamine neurotransmission has been implicated in various forms of cognitive-information processing, the present findings suggest that biochemically depleting central serotonin and catecholamine availability does not alter IT. The absence of effect on IT scores after TD and TPD cannot be explained in terms of insufficient peripheral amino-acid depletion, as the magnitude of plasma precursor reduction is consistent with reported norms (Moore et al., 2000). It is also unlikely that the selection of a female sample in this study would have biased results, as no prior sex differences have been observed in studies relating drug-induced changes to IT performance (Hutchinson et al., 2001; Thompson et al., 2000, 2002). Moreover, TD has been
shown to lower brain serotonin metabolism more in females, thus increasing the likelihood of a potential serotonergic-related effect on IT (Nishizawa et al., 1997). The present results can be contrasted to studies that have reported a facilitation of IT with the cholinomimetics, nicotine and donepezil (cholinesterase inhibitor), and impairment following the administration of the cholinergic–nicotinic receptor antagonist mecamylamine (Hutchinson et al., 2001; Stough et al., 1995; Thompson et al., 2000, 2002). These studies have been interpreted as strengthening early work in AD of a cholinergic involvement in IT (Deary et al., 1991). Degeneration of basal forebrain cholinergic, but not serotonin or catecholamine input to the cortex, has been shown to correlate with severity of cognitive deficits in AD (Sarter and Bruno, 1999). IT performance has also been associated with cognitive symptoms in AD, correlating \( r = 0.81 \) with CAMDEX-cog scores (Deary et al., 1991). Together these findings have provided evidence for cholinergic function in modulating IT, however deficits on this task are also evident in patients with schizophrenia and unipolar depression where gross abnormalities of the cholinergic system are not aetologically implicated (Tsourtos et al., 1995, 2002). Changes in monoamine neurotransmission are believed to play a prominent role in the appearance of symptoms and cognitive deficits in these disorders, yet our results suggest that their influence on IT may be secondary to other factors. For example, based on a cholinergic hypothesis, patients with schizophrenia may perform poorly on this task due to the effects of anticholinergic medications that are often administered to combat neuroleptic drug-induced extrapyramidal side-effects. Similarly, non-specific effects such as effort, motivation and distraction from symptoms have been linked to cognitive slowing in depression and may also explain impairments of IT performance.

Alternatively it could be argued that the choice of manipulation used in this study (i.e. biochemical) may have been too indirect, short lasting or non-selective for monoaminergic neurons in pathways that facilitate cortico-sensory information flow (Morrison et al., 1984). For example, the effects of TD on cognitive processing appear to be selective for tests of learning and episodic memory, which suggests that this manipulation may target discrete networks of high serotonergic innervation (e.g. hippocampus–anterior–thalamic axis) (Riedel et al., 1999; Schmitt et al., 2000). In contrast, the effects of low serotonin on information processing and attention have been inconsistent, with studies reporting beneficial effects of TD on tests of focused and divided attention (Coull et al., 1995), negative effects on speed of visual information processing (RTs) (Sobczak et al., 2002), and no effect on multiple recordings of RT, sustained attention and vigilance (Riedel et al., 1999). Paradoxically, reports of a positive effect of TD on attention have been interpreted as reflecting a possible decrease in serotonin-mediated inhibition of forebrain cholinergic neurons (Schmitt et al., 2000). Neurochemical and behavioural evidence has also indicated that the

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<th>Table 1. Plasma concentration of amino acids</th>
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<td>Amino acid</td>
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<tr>
<td>L-tryptophan</td>
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<td>L-tyrosine</td>
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<td>L-phenylalanine</td>
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Values are given as mean ± S.E.M. in \( \mu \text{mol/l} \).

** \( p < 0.001 \), *** \( p < 0.0001 \).

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<th>Table 2. Information-processing scores at baseline and 5 h after drink administration</th>
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<td>Measure</td>
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<td>Inspection time (ms)</td>
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<td>Total trials</td>
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Values are given as mean ± S.E.M. for IT and the total trials needed to reach the 80% accuracy threshold.
TPD procedure primarily impairs dopamine release in frontostriatal projections, while sparing noradrenergic functions in the reticular core (McTavish et al., 1999). In humans TPD has been associated with deficits on tests of prefrontal cortical integrity (e.g. spatial working memory) but not low-order attentional modalities such as performance on the Rapid Visual Information Processing (RVIP) task (Harmer et al., 2001).

In summary, the efficiency of early-stage visual information processing as measured on the IT task was not affected by an experimental manipulation of brain monoamines in human volunteers. While the IT task has been proposed as a psychophysical index of cognitive slowing in primary cholinergic disorders such as AD (Nathan and Stough, 2001), the present study suggests that its use in evaluating clinical states that are characterized by monoaminergic disturbances may be limited. Further research is needed to explore the influence of other neurochemical systems on IT (e.g. GABA, glutamate), and possible interactions between the monoamine and cholinergic systems.

References


