

Differential Effects of Acute Serotonin and Dopamine Depletion on Prepulse Inhibition and P50 Suppression Measures of Sensorimotor and Sensory Gating in Humans

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Schizophrenia is associated with impairments of sensorimotor and sensory gating as measured by prepulse inhibition (PPI) of the acoustic startle response and P50 suppression of the auditory event-related potential respectively. While serotonin and dopamine play an important role in the pathophysiology and treatment of schizophrenia, their role in modulating PPI and P50 suppression in humans is yet to be fully clarified. To further explore the role of serotonin and dopamine in PPI and P50 suppression, we examined the effects of acute tryptophan depletion (to decrease serotonin) and acute tyrosine/phenylalanine depletion (to decrease dopamine) on PPI and P50 suppression in healthy human participants. In addition, we also examined for the first time, the effects of simultaneous serotonin and dopamine depletion (ie combined monoamine depletion) on PPI and P50 suppression. The study was a double-blind, placebo-controlled cross-over design in which 16 healthy male participants completed the PPI and P50 paradigms under four acute treatment conditions: (a) balanced/placebo control, (b) acute tryptophan depletion, (c) acute tyrosine/phenylalanine depletion, and (d) acute tyrosine/phenylalanine/tryptophan depletion (combined monoamine depletion). Selective depletion of dopamine had no significant effect on either PPI or P50 suppression, whereas selective serotonin depletion significantly disrupted PPI, but not P50 suppression. Finally, the simultaneous depletion of both serotonin and dopamine resulted in significant reduction of both PPI and P50 suppression. We suggest these results can be explained by theories relating to optimal levels of monoaminergic neurotransmission and synergistic interactions between serotonergic and dopaminergic systems for normal 'gating' function. These findings suggest that a dysfunction in both serotonin and dopamine neurotransmission may, in part, be responsible for the gating deficits observed in schizophrenia, and their normalization following administration of atypical antipsychotic drugs.

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INTRODUCTION

A disturbance in information processing has long been regarded as a significant feature of the deficits characteristic of schizophrenia (Braff, 1993; McGhie and Chapman, 1961). In particular, the filtering or 'gating' of sensory information is thought to be disrupted in schizophrenic patients, and this is hypothesized to lead to sensory flooding and

cognitive fragmentation (Braff and Geyer, 1990). Two psychophysiological measures of gating have been of particular interest to researchers in the study of schizophrenia, namely prepulse inhibition (PPI) of the acoustic startle response and P50 suppression of the auditory event-related potential (ERP).

The acoustic startle reflex is a defense response consisting of series of muscular contractions that can be elicited in response to a sudden loud stimulus with abrupt onsets (Landis and Hunt, 1939; Prosser and Hunter, 1936). PPI of the startle reflex refers to an attenuation of this startle reflex that occurs when the evoking stimulus is preceded by a non-startling 'prepulse' by approximately 30–500 ms (Graham, 1975; Hoffman and Flesher, 1963; Ison *et al*,

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1973). In humans, the startle reflex is typically measured via the electrical activity of the orbicularis oculi muscle using electromyography (EMG) (Graham, 1975), and the PPI is typically calculated as a percentage score of the reduction in magnitude of this measure of the startle reflex, with maximal inhibition generally observed with 'lead intervals' of approximately 120 ms (Graham, 1975; Hoffman and Fleshler, 1963; Ison *et al*, 1973). It has now been well documented that patients with schizophrenia display a deficit in PPI (for a review see Cadenhead and Braff, 1999; Braff *et al*, 2001, 2007), which is interpreted as reflecting a failure of 'sensorimotor gating' (Braff and Geyer, 1990), and which may be normalized with the use of atypical antipsychotic drugs (Weike *et al*, 2000; Hamm *et al*, 2001; Kumari and Sharma, 2002; Kumari *et al*, 2007).

P50 is a positive deflection in the auditory ERP that occurs approximately 50 ms after the presentation of an auditory stimulus. In a double-click (or double-tone) paradigm, two clicks are presented 500 ms apart, and normal individuals show a reduced response to the second click (Click 2 or S2) relative to the amplitude of the first click (Click 1 or S1) (termed P50 suppression) with interstimulus intervals (ISIs) between 500 and 2000 ms. Analogous to PPI, the second stimulus is 'gated' or inhibited by the initial stimulus. The P50 is measured via electroencephalography (EEG), where it is maximal at the vertex, and suppression is described as a ratio (ie Click 2 P50 amplitude/Click 1 P50 amplitude) or difference score (ie Click 2 P50 amplitude–Click 1 P50 amplitude). Normal control participants normally exhibit suppression in the range of 50–70% (Adler *et al*, 1999), while it has been demonstrated that patients with schizophrenia display significantly lower P50 suppression (Adler *et al*, 1982; Boutros *et al*, 1991; Light *et al*, 2000; Ward *et al*, 1996; Yee and White, 2001; Braff *et al*, 2007), which is interpreted as reflecting a deficit in 'sensory gating' (Adler *et al*, 1982). Analogous to the PPI findings, there is also some evidence that P50 suppression deficits in schizophrenia may be normalized with the use of atypical antipsychotic drugs (Light *et al*, 2000; Nagamoto *et al*, 1996, 1999; Adler *et al*, 2004; Becker *et al*, 2004).

Although PPI and P50 suppression are thought to reflect similar or related constructs, the actual relationship between the two is still unclear, with recent studies suggesting that these paradigms may be assessing different neural mechanisms (Brenner *et al*, 2004; Oranje *et al*, 2006). For example, it has been suggested that PPI and P50 suppression are related only insofar as hippocampal circuitry is involved in both processes (Swerdlow *et al*, 2000).

The neurochemical basis of schizophrenia has been linked to dysfunction in a number of neurotransmitter systems, including the glutamatergic, dopaminergic, and serotonergic systems (for reviews see Laruelle *et al*, 2003; Geyer *et al*, 2001; Dean, 2003). However, to date, the exact mechanisms of their role in gating dysfunctions in schizophrenia have not been determined. Animal studies have shown that sensorimotor gating, as measured by PPI, can be modulated by a number of neurotransmitter systems including dopaminergic, glutamatergic, serotonergic, GABAergic, and cholinergic systems (for a review see Geyer *et al*, 2001). However, these studies have been fairly inconsistent, both in terms of their findings and in the

parameters used to measure gating (eg different prepulse intensities and prepulse to pulse intervals in PPI, lack of uniformity across laboratories in P50 peak detection, EEG processing, and filtering and differences in findings using different strains of animals) (Geyer *et al*, 2001). Pharmacological research on PPI and P50 suppression in humans is scarce, and discrepancies between animal and human studies on sensorimotor and sensory gating have also been documented, particularly for the serotonergic system (for a discussion see Hammer *et al*, 2007). Hence, it is critical that studies in humans are conducted to examine the neurochemistry of both sensorimotor and sensory gating.

Although it has been extensively hypothesized that serotonin and dopamine play an important role in the pathophysiology and treatment of Schizophrenia, their role in modulating PPI and P50 suppression in humans is yet to be fully clarified. Studies investigating the effects of serotonergic modulation on PPI in healthy humans have been inconclusive. Enhancing serotonin neurotransmission with MDMA (3,4-methylenedioxy-*N*-methylamphetamine or ecstasy), a presynaptic serotonin releaser (Liechti *et al*, 2001), and the 5-HT_{2A/1A} agonist, psilocybin (Gouzoulis-Mayfrank *et al*, 1998; Vollenweider *et al*, 1999), has been shown to increase PPI. However, the effects of psilocybin on PPI may be dependant on the ISI, with another study finding a decrease in PPI at ISIs of 30 ms, no effects at ISIs of 60 ms, and an increase in PPI at 120–2000 ms (Vollenweider *et al*, 2007). On the other hand, reducing serotonergic neurotransmission with ketanserin (a non-selective 5-HT₂ receptor antagonist) (Graham *et al*, 2002) or buspirone (a 5-HT_{1A} partial agonist acting presynaptically) (Gogos *et al*, 2006) has been found to reduce PPI. Nevertheless, other studies have found no effects on PPI following enhancement of central serotonin levels with the administration of serotonin reuptake inhibitors, fenfluramine (Abel *et al*, 2007), fluvoxamine (Phillips *et al*, 2000b), citalopram (Liechti *et al*, 2001), and escitalopram (Jensen *et al*, 2007). To our knowledge, the effects of serotonergic modulation on P50 suppression in healthy humans has only been investigated once, with findings showing a decrease in P50 suppression with the psychedelic plant *ayahuasca*, which contains many active constituents including *N,N*-dimethyltryptamine, a 5-HT_{2A/2C} receptor agonist (Riba *et al*, 2002). Given the rich pharmacology of *ayahuasca*, this study does not address the direct contribution of the serotonergic system in the regulation of P50 suppression. Like the serotonergic system, the effect of dopaminergic modulation on both PPI and P50 in healthy human subjects has also been inconsistent. The dopamine D₂ receptor agonist bromocriptine (Abduljawad *et al*, 1998, 1999), the D₁/D₂ agonist, pergolide (Bitsios *et al*, 2005), the D₃ agonist, ropinirole (Giakoumaki *et al*, 2007), and the dopamine reuptake inhibitor and releaser, amphetamine (Hutchison and Swift, 1999) and amantadine (Bitsios *et al*, 2005), have all been shown to reduce PPI, whereas other studies have reported that dopamine agonists including bromocriptine and L-dopa have no effects on PPI (Kumari *et al*, 1998; Swerdlow *et al*, 2002a, b). Similarly, amphetamine has been shown to decrease P50 suppression (Light *et al*, 1999), whereas other studies report no effects of enhancing dopamine neurotransmission with bromocriptine and the

dopamine precursor L-dopa on P50 suppression (Oranje *et al*, 2004).

One method that has been increasingly employed in humans to manipulate central serotonin and dopamine neurotransmission is the method of amino-acid precursor depletion (Reilly *et al*, 1997). On the basis of acute precursor restrictions, endogenous neurotransmitter release is reduced through an ingested suspension of amino acids that lack certain neurotransmitter precursors. In humans, acute tryptophan depletion (ATD) has been shown to acutely decrease concentrations of serotonin and its metabolites (Carpenter *et al*, 1998; Moja *et al*, 1988; Nishizawa *et al*, 1997; Williams *et al*, 1999), and has been shown to consistently impair serotonin-dependent processes such as memory consolidation and learning (Harrison *et al*, 2004; Sambeth *et al*, 2007). Using this method, serotonin depletion was found to decrease PPI in healthy humans (Phillips *et al*, 2000a). On the other hand, acute tyrosine/phenylalanine depletion (ATPD) has been shown to selectively decrease dopamine synthesis and release (Jaskiw and Bongiovanni, 2004; Leyton *et al*, 2000; McTavish *et al*, 1999a,b, 2001a,b; Mehta *et al*, 2005; Montgomery *et al*, 2003), and impair dopamine-dependent cognitive processes such as working memory (Harmer *et al*, 2001; Harrison *et al*, 2004). The effects of dopamine depletion via ATPD on PPI and P50 suppression are yet to be determined.

To further explore the role of serotonin and dopamine in sensorimotor and sensory gating, we examined the effects of ATD (to decrease serotonin) and ATPD (to decrease dopamine) on PPI and P50 suppression in healthy human participants. In addition, we also examined for the first time, the effects of simultaneous dopamine and serotonin depletion (ie combined monoamine depletion, CMD) on PPI and P50 suppression. CMD has been shown to simultaneously deplete tryptophan, tyrosine, and phenylalanine to levels that are expected to modulate central dopaminergic and serotonergic function (Nathan *et al*, 2004; Matrenza *et al*, 2004). Given the inconsistencies in previous findings with regard to the effects of serotonin and dopamine on PPI and P50 suppression, we made no directional hypotheses. No predictions were made concerning the effects of combined dopamine and serotonin depletion, given the novel nature of this investigation.

METHODS

Participants

Sixteen healthy non-smoking male volunteers, aged 20–41 years ($M = 26$, 13 years, $SD = 6.70$ years), were included in the study. Participants were recruited through local and university advertisements, and were considered for inclusion if they were non-smoking, not currently taking any medications, had no personal or family history of psychiatric disorders, had no history of substance abuse, and had no history of head injury or neurological disorders. All candidates underwent a semi-structured medical examination and clinical interview performed by a medical physician before participation, to confirm that they were physically and psychiatrically suitable and to ensure that the inclusion criteria were met. Also, all participants gave

written informed consent for participation in the study, which was approved by the Swinburne University Human Research Ethics Committee.

Study Design

This study was a double-blind, placebo-controlled, cross-over design in which each participant was tested under four acute treatment conditions; (a) 104 g nutritionally balanced placebo control treatment (BAL), (b) ATD for serotonin depletion, (c) ATPD for dopamine depletion, and (d) acute tyrosine, phenylalanine, and tryptophan depletion (CMD) for depletion of dopamine and serotonin. The assignment for order of completion of each treatment for each individual was randomized using a computerized randomization program. Completion of each treatment was separated by a minimum 5-day washout period.

Amino-Acid Composition

The amino-acid composition for the depletion treatments was based on the 104 g balanced mixture developed by Young *et al* (1985), and modified for the CMD as outlined by Nathan *et al* (2004). In the current study, the amino-acid mixture for the balanced control treatment consisted of 5.5 g of L-alanine, 3.2 g of glycine, 3.2 g of L-histidine, 8.0 g of L-isoleucine, 13.5 g of leucine, 11.0 g of L-lysine monohydrochloride, 5.7 g of L-phenylalanine, 12.2 g of L-proline, 6.9 g of L-serine, 6.5 g of L-threonine, 2.3 g of L-tryptophan, 6.9 g of L-tyrosine, and 8.9 g of L-valine. Additionally, 4.9 g of L-arginine, 2.7 g of L-cysteine, and 3.0 g of L-methionine were encapsulated in 22 gelatin capsules and administered separately due to their unpleasant taste. All treatment mixtures were composed of the same amino acids as in the BAL treatment, but the ATPD mixture was deficient of L-tyrosine and L-phenylalanine for the depletion of dopamine, and the ATD mixture was deficient of L-tryptophan for the depletion of serotonin. The CMD treatment was deficient of L-tryptophan, L-tyrosine, and L-phenylalanine for the simultaneous depletion of dopamine and serotonin.

The powdered suspension was mixed with 180 ml of orange juice immediately before oral ingestion and following administration of the capsules. Participants were advised to swallow the drink as quickly as possible, given the unfamiliar taste and texture of the mixture.

Procedure

Before each testing session, participants were required to adhere to a 24-h low-protein diet, with their total protein consumption to be less than 20 g (Young *et al*, 1985; Harrison *et al*, 2004). Participants were also required to fast from 1900 hours the evening before each testing day, with the exception of drinking water. A low-protein diet and fasting is thought to enhance monoamine depletion and reduce variability in baseline monoamine levels (Reilly *et al*, 1997). On arrival for testing, participants were required to complete the Visual Analog Mood Scales (VAMSs) to establish baseline mood, and then had a small sample of blood taken (12 ml) to establish baseline amino-acid levels.

Participants were then administered the amino-acid drink and capsules, which took approximately 10 min.

During the next 5 h, participants rested and were instructed to refrain from any physical activity. Participants were permitted to study or utilize neutral videos, books, and magazines that were provided. Approximately 2 h post amino-acid ingestion, participants were provided with a low-protein snack of carrot and apple. Four and a half hours post ingestion, participants were again given the VAMSs to examine mood changes following treatment, and were required to give another sample of blood (12 ml) to establish the amino-acid depletion levels. Five hours post amino-acid depletion, participants completed the tasks associated with the measurement of PPI and P50 suppression. Participants were seated in a comfortable chair, approximately 60 cm from a computer screen, tested for hearing, and given instructions for each test paradigm. The 5-h latency period was chosen to coincide with the timing of the maximal pharmacokinetic and physiological effects of monoamine depletion, as determined in the previous research (Carpenter *et al*, 1998; Harrison *et al*, 2004; Harmer *et al*, 2001; Leyton *et al*, 2000; Matrenza *et al*, 2004; McTavish *et al*, 1999a; Moja *et al*, 1988; Mehta *et al*, 2005; Nathan *et al*, 2004; Nishizawa *et al*, 1997; Sambeth *et al*, 2007; Williams *et al*, 1999). Upon conclusion of the testing procedure, participants were provided with high-protein snacks to replenish their amino-acid levels. Participants resumed their regular diet between successive testing sessions.

Prepulse Inhibition of the Acoustic Startle Response

The acoustic startle response was measured from the orbicularis oculi muscle EMG activity, recorded as the difference between two 6 mm electrodes placed below the right eye. Stimuli were generated with a Neuroscan STIM2 audio system and software (NeuroScan Labs, Sterling, VA), and presented to participants binaurally via EAR insert earphones (Aearo Company Auditory System, Indianapolis, IN). EMG activity was digitized continuously at 2000 Hz, amplified and band-pass filtered (0.05–500 Hz) using a Neuroscan Synamps system.

Acoustic startle testing was similar to the procedure used by Gogos *et al* (2006) and comprised a total of 24 trials consisting 8 trials of the startle stimuli (ie pulse alone (PA)), to allow for habituation in order to obtain an accurate measure of startle amplitude (Gogos *et al*, 2006), 8 trials of PA stimuli, and 8 trials each of PA and prepulse stimuli (ie prepulse-PA (PP)), with the trials of PA and PP presented in a pseudo-random order. The inter-trial intervals ranged from 16 to 24 s ($M = 20$ s). Throughout the testing session 70 dB of white noise continued, following an initial 1-min acclimation period. The startle pulse was a 40 ms burst of white noise, 38 dB above background (108 dB), with < 1 ms rise/fall time, and prepulses were 20 ms bursts of white noise, 15 dB above the background noise (85 dB), and preceding the startle pulse by 60 ms (lead interval). A visual task was given to the participants during the startle paradigm to control their attention—participants were instructed to look at the computer screen and press a keypad when a face without a nose appeared, as opposed to a face with a nose. The advantage of the task is that it

controls the level of attentional demand, as attention has been shown to modulate PPI and it has been suggested that in the case of uninstructed studies, attention is unconstrained and hence the effects of attention on PPI are unknown (Kedzior and Martin-Iverson, 2007).

The EMG recordings were epoched (–80 to 300 ms post stimulus), band-pass filtered (10–200 Hz), rectified, smoothed (over five adjacent data points and three consecutive passes), and baseline corrected as indicated by Anokhin *et al* (2003). The magnitude of the startle response was defined as the peak EMG response within 20–120 ms post stimulus (Balaban *et al*, 1986), as determined by the NeuroScan software. %PPI was calculated as $(PA - PP / PA) \times 100$, with higher percentages indicating greater inhibition (ie more sensorimotor gating). Following methods used in our previous studies (Gogos *et al*, 2006), two participants were classified as ‘non-responders’ and excluded from further statistical analysis, as the peak startle amplitude was less than 0.3 (arbitrary units) in the placebo treatment condition. A third participant was also classified as a non-responder as they did not demonstrate PPI in the placebo treatment condition (ie subjects needed to demonstrate pre-pulse inhibition in the placebo treatment condition to examine the effects of dopamine and serotonin depletion on prepulse inhibition).

P50 Suppression of the ERP

EEG was recorded using an electrocap (tin electrodes) with 62 scalp sites located according to the International 10–20 System. Impedances were below 5 k Ω at the start of the recording. EEG data at the Cz electrode (ie where the P50 ERP has been shown to have maximum activity; Clementz *et al*, 1998), located at the vertex, was continuously digitized at 500 Hz, amplified and band-pass filtered (0.01–100 Hz) using the Neuroscan Synamps system.

Two mastoid electrodes placed behind the left and right ears were used as reference electrodes. Fifty-two 80 dB click pairs with a 500 ms interclick interval were relayed to the participant binaurally through ear inserts, every 8–12 s ($M = 10$ s). Clicks were 1 ms duration square waves with near instantaneous rise and fall times (< 1 ms). Background noise was continuous 70 dB white noise, as in the PPI recording. Participants were given the same nose/no nose task as in the PPI paradigm, to control for attention. EEG data were epoched from –200 to 500 ms post stimulus, continuously digitized at 500 Hz with a 10–47 Hz bandpass (24 dB/octave roll-off). Before averaging, epochs were manually inspected and rejected if they contained substantial movement artifacts. The epoched data were then averaged; averages were calculated for each participant in each treatment group, and for the response to the first stimulus, and also for the second stimulus separately.

The P50 auditory evoked potential was chosen based on a few criteria. The P50 in response to the onset of Click 1 (SI, conditioning click) was taken as the most positive peak occurring 38–78 ms post stimulus/click (Croft *et al*, 2004). The P50 peak needed to be preceded by a negative deflection, Na, occurring between 25 and 50 ms, and a positive deflection, Pa, occurring between 15 and 40 ms post stimulus (Croft *et al*, 2004). Where Pa or Na components could not be identified, the larger positive deflection

occurring between 40 and 80 ms was considered to be the P50 waveform. Additionally, the P50 peak had to occur within ± 15 ms of the P50 identified in the grand average, and the Na and Pa had to occur within ± 10 ms of the Na and Pa deflections in the grand average. For the second click (S2, test click), the P50 peak was selected as the most positive wave occurring during a latency range equal to the latency of the conditioning response ± 10 ms. These criteria for latency were used to help ensure that the paired responses represented the same waveform (Nagamoto *et al*, 1991). In addition to the above criteria, the P50 peaks had to exhibit positive fronto-central distributions, which were manually classified using two-dimensional topographic maps (Croft *et al*, 2004). P50 amplitude was defined as the difference between the P50 peak and the preceding negative trough, for each of the conditioning and test P50. P50 suppression ratio was calculated according to the following formula: $((1 - S2/S1) \times 100)$, where S2 is the test P50 amplitude and S1 is the conditioning P50 amplitude. Lower P50 suppression values indicate reduced sensory gating. Two participants were classified as 'outliers' because they had ratios greater than 3 SD from the mean, and were excluded from further analysis.

Subjective Mood Assessment

Subjective mood ratings were obtained using the VAMSs (Bond and Lader, 1974). The VAMS consists of 16 bipolar scales, anchored at each end of a 100 mm line. In factor analyses, these scales reduce to three subscales: alertness (nine items), contentedness (five items), and calmness (two items).

Biochemical Analysis

Upon collection, the venous blood samples (12 ml) were separated by centrifugation for 20 min at 3000 r.p.m. and the resulting plasma stored at -20°C . Using precolumn derivatization with 6-aminoquinolyl-*N*-hydroxysuccinimide carbamate (AQC), concentrations in plasma of the free amino acids tryptophan (TRP), tyrosine (TYR), phenylalanine (PHE), valine (VAL), leucine (LEU), and isoleucine (ILE) were then calculated. The derivatives were then separated and quantified by reversed-phase high-performance liquid chromatography (HPLC) (Cohen, 2001). The amino acids (with the exception of TRP) were detected by fluorescence, whereas TRP required UV detection. VAL, LEU, and ILE levels were analyzed for the purpose of calculating the ratio of plasma TRP, TYR, or PHE, to these other large neutral amino acids (LNAAAs). The ratio of precursors to other LNAAAs has been suggested to be a more accurate indicator of central precursor depletion than absolute plasma precursor levels, due to the competition between the LNAAAs for brain entry via the same AA transporter (Oldendorf and Szabo, 1976).

Before derivatization, the plasma samples (100 μl) were diluted 1:1 with internal standard solution and deproteinized by ultrafiltration through a membrane with a 10 kDa nominal molecular weight cutoff (Ultrafree MC with PL-10 membrane, Millipore, MA, USA). The filtrate (100 μl) was then put through AQC derivatization and HPLC analysis

using the Waters AccTag amino-acid analysis system (Waters Corporation, MA, USA) (Cohen, 2001).

Statistical Analysis

As the biochemical data were not normally distributed and could not be transformed to normality, this was analyzed with non-parametric Friedman's tests. Significant results were followed up with the Wilcoxon's signed ranks test.

PPI data were normalized using the inverse log transformation $t_data = \ln(300 - \text{data})$. To examine the amount of PPI, a paired samples *t*-test with trial type (PA or PP) as the within-subject factor was conducted on the data from the balanced placebo control treatment. %PPI scores and PA startle magnitudes were then analyzed with separate one-way repeated measures ANOVAs with treatment (BAL, CMD, ATD, ATPD) as the within-subject factor. Similarly, to determine whether P50 suppression occurred in the present sample, a paired sample *t*-test with click type (S1 or S2) the within-subject factor was conducted on the P50 data from the balanced placebo control treatment. P50 ratio scores were then analyzed using a one-way repeated measures ANOVA with treatment as the within-subject variable.

VAMS data were analyzed using a 4 (treatment: BAL, ATD, ATPD, CMD) by 3 (subscale: alertness, contentedness, calmness) by 2 (time: baseline, post-treatment) repeated measures ANOVA.

RESULTS

Amino-Acid Concentrations

Friedman's test showed a significant effect of treatment on the plasma levels of the amino acids (tryptophan, tyrosine, and phenylalanine) ($\chi^2(23) = 148.41$; $p = 0.0004$). Follow-up Wilcoxon's signed ranks tests (with significance set at $p < 0.05$) revealed significant increases in all amino acids post administration of the BAL treatment, and significant decreases in all amino acids post administration of the CMD treatment, when compared to baseline concentrations of amino acids. Following ATD, there was a significant decrease in the concentration of TRP and a significant increase in PHE concentration, but no significant change in concentration of TYR, when compared to baseline levels. After the ATPD treatment there was a significant increase in TRP levels, as well as significant decreases in TYR and PHE levels, when compared to baseline concentrations. For percentages see Table 1.

A separate Friedman's test also showed a significant effect of treatment on the amino-acid ratios ($\chi^2(23) = 138.06$, $p = 0.0004$). Follow-up Wilcoxon's signed ranks test (with significance set at $p < 0.05$, two-tailed) revealed that after the BAL treatment, there was a small but significant decrease in the ratio of TYR: Σ LNAAAs, but no significant change in the ratios of TRP: Σ LNAAAs or PHE: Σ LNAAAs, when compared to baseline amino-acid ratios. Following the CMD treatment, there was a significant reduction from baselines in all amino-acid ratios. Following ATD, there was significant reduction in the ratio of TRP: Σ LNAAAs; however, there were no significant decreases in the ratio of TYR: Σ LNAAAs or PHE: Σ LNAAAs, when compared to baseline ratios. Lastly,

Table 1 Plasma Concentrations of Amino Acids ($\mu\text{mol l}^{-1}$) (Mean, SD)

Amino acid	Treatment condition	Baseline	4 h post-treatment	Percent change
Plasma-free TRYP	BAL	4.53 (1.88)	10.94 (3.42)	141.50**
	CMD	4.30 (1.68)	1.37 (0.52)	-68.14**
	ATD	5.10 (1.61)	0.80 (0.23)	-84.31**
	ATPD	4.23 (1.92)	15.07 (7.78)	256.26**
Plasma TYR	BAL	49.06 (11.35)	97.41 (27.26)	98.55**
	CMD	47.33 (10.83)	10.60 (3.33)	-77.60**
	ATD	65.49 (46.78)	96.74 (36.59)	47.72
	ATPD	46.73 (14.02)	12.93 (4.42)	-72.33**
Plasma PHE	BAL	44.96 (9.31)	101.74 (43.86)	126.29**
	CMD	43.90 (8.77)	8.04 (3.12)	-81.69**
	ATD	50.31 (14.51)	114.37 (52.31)	127.33*
	ATPD	41.76 (9.22)	7.77 (1.76)	-81.39**
TRP/ Σ LNAAs	BAL	0.015 (0.006)	0.012 (0.003)	-20.00
	CMD	0.015 (0.005)	0.002 (0.001)	-86.67**
	ATD	0.015 (0.005)	0.001 (0.001)	-93.33**
	ATPD	0.014 (0.008)	0.016 (0.006)	14.29
TYR/ Σ LNAAs	BAL	0.162 (0.031)	0.109 (0.024)	-32.72**
	CMD	0.161 (0.033)	0.015 (0.005)	-90.68**
	ATD	0.162 (0.030)	0.131 (0.060)	-19.14
	ATPD	0.149 (0.059)	0.015 (0.005)	-89.93**
PHE/ Σ LNAAs	BAL	0.149 (0.022)	0.111 (0.033)	-25.50
	CMD	0.149 (0.023)	0.011 (0.004)	-92.62**
	ATD	0.142 (0.034)	0.140 (0.034)	-1.41
	ATPD	0.134 (0.027)	0.009 (0.003)	-93.28**

ATD, acute tryptophan depletion condition; ATPD, acute tyrosine/phenylalanine depletion condition; BAL, balanced condition; CMD, combined monoamine depletion condition; LNAAs, large neutral amino acids.

* $p < 0.05$; ** $p < 0.02$.

following the ATPD condition, there were significant reductions in the ratio of TYR: Σ LNAAs and PHE: Σ LNAAs; however, there was no significant change in the ratio of TRP: Σ LNAAs, when compared to baseline ratios. For percentages see Table 1.

To establish whether depletion levels achieved after the CMD treatment were equivalent to those achieved after the ATD and ATPD treatments, percentage change of the amino-acid ratios ((post-pre/pre)*100) was compared across the treatment conditions. Wilcoxon's signed ranks test (with significance set at $p < 0.05$) revealed no significant difference in percentage change in the ratios of TYR: Σ LNAAs or PHE: Σ LNAAs between ATPD and CMD treatments. Additionally, there was no significant difference in the percentage change of the ratio of TRP: Σ LNAAs, between the ATD and CMD treatments.

Prepulse Inhibition

A paired samples t -test comparing PA and PP magnitudes in the BAL treatment revealed larger startle responses on PA trials when compared to PP trials (ie significant PPI) ($t(12) = 2.40$, $p = 0.03$) (Figure 1). A one-way repeated measures ANOVA revealed no significant difference in startle magnitude (ie PA trials) across the four treatment conditions ($F(3, 36) = 1.15$, $p = 0.27$; Figure 1). In contrast, a

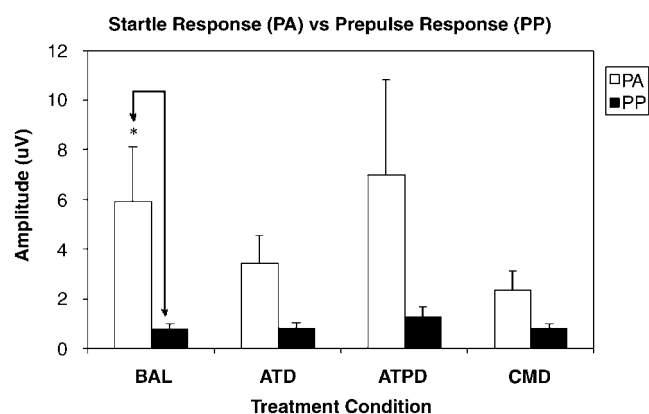


Figure 1 Mean PA and PP startle magnitude in the ATD, ATPD, and CMD treatment conditions compared with the BAL treatment. *Significant difference between PA and PP in the BAL treatment ($p < 0.05$). ATD, tryptophan depletion; ATPD, tyrosine/phenylalanine depletion; BAL, placebo control; CMD, combined tryptophan, tyrosine, and phenylalanine depletion; PA, pulse alone; PP, prepulse. Results expressed as mean \pm SEM.

one-way repeated measures ANOVA revealed a significant main effect of treatment on %PPI ($F(3, 36) = 2.92$, $p = 0.047$, partial $\eta^2 = 0.20$). Simple planned contrasts indicated that there were significant reductions in %PPI after both the

CMD treatment ($F(1, 12) = 5.66$, $p = 0.035$, partial $\eta^2 = 0.32$), and the ATD treatment ($F(1, 12) = 4.78$, $p = 0.049$, partial $\eta^2 = 0.29$), when compared to the BAL treatment. However, there was no significant change in %PPI after the ATPD treatment ($F(1, 12) = 3.14$, $p = 0.102$; Figure 2). Furthermore, simple planned contrasts showed no significant differences in the latency to startle peak in the CMD ($F(1, 12) = 1.12$, $p = 0.311$), ATD ($F(1, 12) = 0.145$, $p = 0.71$),

or ATPD treatments ($F(1, 12) = 4.43$, $p = 0.057$) when compared to the BAL treatment condition.

P50 Suppression

As with PPI, a paired samples t -test comparing T1 and T2 amplitudes in the BAL treatment revealed larger P50 amplitudes to T1 than T2 (ie significant P50 suppression) ($t(12) = 5.52$, $p = 0.0004$; Figures 3 and 4). A one-way repeated measures ANOVA of the T2/T1 ratio revealed a

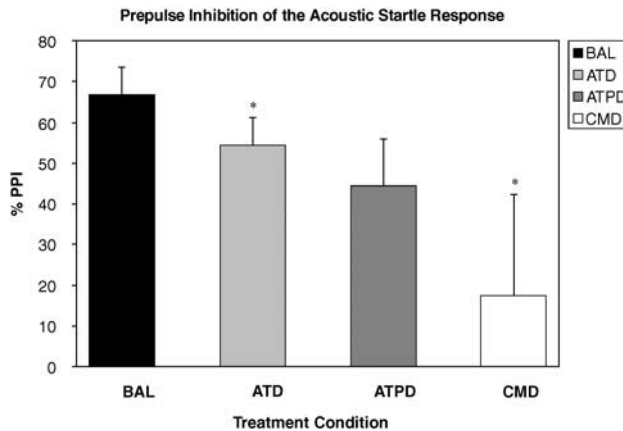


Figure 2 Percentage PPI of startle response in the ATD, ATPD, and CMD treatment conditions compared with the BAL treatment. ATD, tryptophan depletion; ATPD, tyrosine/phenylalanine depletion; BAL, placebo control; CMD, combined tryptophan, tyrosine, and phenylalanine depletion. *Significant reduction in percentage inhibition in the ATD and CMD treatments when compared to the BAL treatment ($p < 0.05$). Results are expressed as mean \pm SEM.

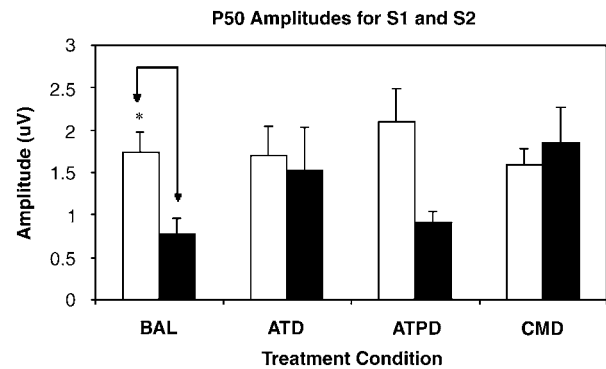


Figure 4 Mean P50 amplitudes for Click 1 (S1) and Click 2 (S2) in the ATD, ATPD, and CMD treatment conditions compared with the BAL treatment. ATD, tryptophan depletion; ATPD, tyrosine/phenylalanine depletion; BAL, placebo control; CMD, combined tryptophan, tyrosine, and phenylalanine depletion. *Significant difference between amplitude of S1 compared to amplitude of S2 in the BAL treatment ($p < 0.001$). Results are expressed as mean \pm SEM.

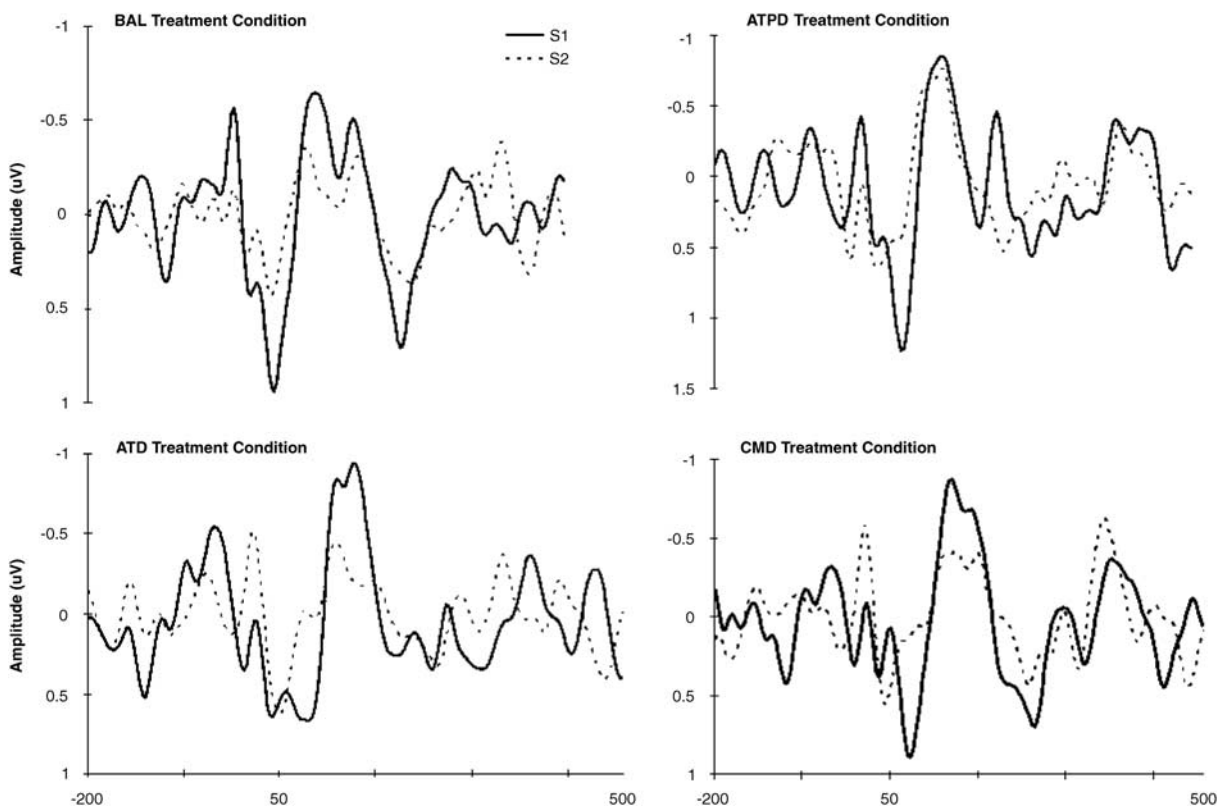


Figure 3 Grant average P50 waveforms for the ATD, ATPD, and CMD treatment conditions compared with the BAL treatment condition.

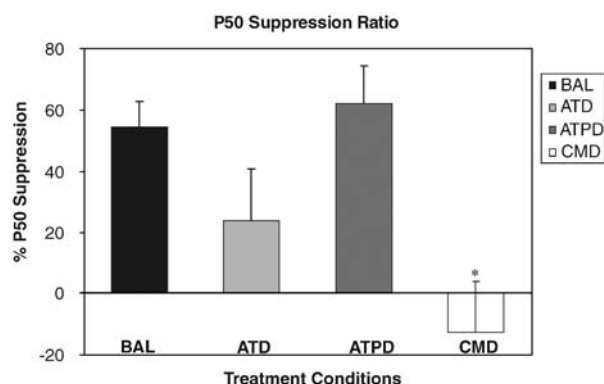


Figure 5 P50 suppression ratio in the ATD, ATPD, and CMD treatment conditions compared with the BAL treatment. ATD, tryptophan depletion; ATPD, tyrosine/phenylalanine depletion; BAL, placebo control; CMD, combined tryptophan, tyrosine, and phenylalanine depletion. *Significant decrease in P50 suppression in the CMD compared to the BAL treatment (* $p = 0.00$). Results are expressed as mean \pm SEM.

significant main effect of treatment ($F(3,36) = 4.63$, $p = 0.008$, partial $\eta^2 = 0.28$). Simple planned contrasts indicated that there was a significant increase in the P50 ratio (ie decrease in P50 suppression) after the CMD treatment condition, when compared with the balanced control treatment ($F(1,13) = 24.49$, $p = 0.00$, partial $\eta^2 = 0.36$); however, there was no difference in the P50 ratio after either the ATD ($F(1,13) = 3.44$, $p = 0.086$) or ATPD ($F(1,13) = 0.23$, $p = 0.64$) treatments (Figure 5).

Subjective Mood Assessment

Repeated measure ANOVA showed no significant treatment by time interaction ($F(3,39) = 0.59$, $p = 0.63$), and no VAMS subscale by treatment by time interaction ($F(6,78) = 1.35$, $p = 0.09$), suggesting no significant changes in the mood following any of the treatment conditions for VAMS subscales, alertness, contentedness, and calmness.

DISCUSSION

The current study investigated the effects of selective and combined serotonin and dopamine depletion on measures of 'sensorimotor gating' (ie PPI) and 'sensory gating' (ie P50 suppression), in healthy male subjects. Depletion of serotonin via tryptophan depletion significantly disrupted PPI, but had no effect on P50 suppression, whereas dopamine depletion via tyrosine/phenylalanine depletion had no significant effect on either PPI or P50 suppression. Lastly, the simultaneous depletion of dopamine and serotonin via tryptophan, tyrosine, and phenylalanine depletion resulted in significant reductions in both PPI and P50 suppression. These findings were observed independent of any mood effects and provide evidence for differential modulation of PPI and P50 suppression measures of sensorimotor and sensory gating, respectively, by both serotonin and dopamine in humans.

Serotonin Depletion

ATD induced a 93% decrease in the ratio of tryptophan to other LNAAs, a decrease that is comparable to, if not exceeding, that obtained in other studies (Schmitt *et al*, 2000; Sobczak *et al*, 2002; Sambeth *et al*, 2007). Furthermore, decreases of such a magnitude have been shown to significantly affect brain serotonin synthesis (Moja *et al*, 1988; Nishizawa *et al*, 1997), CSF concentrations of serotonin metabolites (Carpenter *et al*, 1998; Williams *et al*, 1999), and serotonin-dependent cognitive processes (Sambeth *et al*, 2007). Following ATD we observed impairments in sensorimotor gating, as evidenced by a reduction in PPI. This finding directly supports a number of studies that have similarly found a decrease in PPI following a reduction in serotonergic neurotransmission in healthy humans, with ATD (Phillips *et al*, 2000a), the 5-HT₂ receptor antagonist ketanserin (Graham *et al*, 2002), and the 5-HT_{1A} partial agonist buspirone (Gogos *et al*, 2006). The findings also concur with a number of studies that report the opposite effect (ie an increase in PPI with enhancement of serotonergic neurotransmission) with MDMA (Liechti *et al*, 2001) and the 5-HT_{2A/1A} agonist psilocybin (Gouzoulis-Mayfrank *et al*, 1998; Vollenweider *et al*, 1999). However, serotonergic manipulation has not consistently modulated PPI in all studies in humans, with some studies reporting no effects on PPI following acute enhancement of synaptic serotonin with the serotonin reuptake inhibitors, fenfluramine (Abel *et al*, 2007), fluvoxamine (Phillips *et al*, 2000b), citalopram (Liechti *et al*, 2001), and escitalopram (Jensen *et al*, 2007); and other studies reporting a reduction in PPI or no effects on PPI (depending on the ISI) with psilocybin (Vollenweider *et al*, 2007).

While the reason for this inconsistency is unclear, there are some important possibilities worth discussing. First, it is possible that differences between studies may relate to the selectivity or potency of the drugs or manipulations for the serotonergic system. It could be argued that the positive effects of MDMA and psilocybin may be mediated by their effects on other neurotransmitter systems, including dopamine or noradrenaline, rather than their serotonergic actions. However, this is unlikely as we and others have shown a decrease in PPI following ATD (in this study and Phillips *et al*, 2000a) and with the 5-HT_{1A} agonist, buspirone (Gogos *et al*, 2006). It is more likely that effects are related to the potency of serotonergic modulation. Indeed animal studies have shown evidence for dose-dependant effects of serotonin depletion (Prinssen *et al*, 2002) and serotonin agonists (Geyer *et al*, 2001; Vollenweider *et al*, 2007) on PPI. Secondly, it is possible that differences between studies may be related to the stimulus characteristics of the PPI paradigm (eg the interval between prepulse and pulse) and their subsequent sensitivity to serotonergic manipulation. In support, Vollenweider *et al* (2007) recently reported an effect on PPI that was dependent on the interval between prepulse and pulse (ie lead interval), with psilocybin reducing PPI at short (30 ms), having no effects at medium (60 ms), and increasing PPI at long (120–2000 ms) intervals. Similar effects have also been reported with MDMA (Liechti *et al*, 2001). Finally, differences between studies may be related to methodological differences in the samples selected. Only a few studies, including the current study,

have controlled for smoking (Liechti *et al*, 2001; Gogos *et al*, 2006) and menstrual cycle phase (Liechti *et al*, 2001; Gogos *et al*, 2006; Vollenweider *et al*, 2007). This is critical as both smoking (Della Casa *et al*, 1998) and changes in menstrual cycle phase (Swerdlow *et al*, 1997) have been reported to influence PPI.

In contrast, after ATD we did not observe a significant difference in P50 suppression, suggesting that P50 suppression is not modulated by acute changes in serotonergic neurotransmission. This finding is inconsistent with a report showing a reduction in P50 suppression with the 5-HT_{2A/2C} receptor agonist *ayahuasca* (Riba *et al*, 2002). However, the latter findings should be interpreted with caution, as *ayahuasca* has multiple pharmacological actions in addition to its 5-HT_{2A/2C} receptor agonistic properties, and hence the P50 suppression reduction could not be attributed specifically to serotonergic effects. Two other studies in patients with schizophrenia reported increases in P50 suppression with the 5-HT₃ antagonists odansetron and tropisetron (Adler *et al*, 2005; Koike *et al*, 2005), providing some evidence for serotonergic regulation of P50 suppression. However, the latter studies were conducted in patients with schizophrenia who were on atypical antipsychotics and these drugs have multiple pharmacological effects, making it difficult to elucidate the exact mechanisms responsible for the P50 increases. A likely possibility is that the effects are mediated by modulation of the cholinergic system. A link between P50 suppression and nicotinic receptors has been reported previously (Adler *et al*, 1986, 1992; Freedman *et al*, 1997), and tropisetron has been shown to modulate P50 suppression via effects on nicotinic receptors (Hashimoto *et al*, 2005).

In summary, current findings provide evidence for neurochemical differentiation with regard to the effects of selective serotonergic modulation on PPI and P50 suppression. These findings add to the growing body of evidence suggesting that these paradigms may in fact be assessing different neural mechanisms.

Dopamine Depletion

ATPD resulted in an 83% reduction in the ratio of tyrosine to other LNAAs, and a 93% reduction in the ratio of phenylalanine to other LNAAs. These depletion levels are equivalent to those observed using ATPD in previous studies (Harmer *et al*, 2001; Leyton *et al*, 2000). Furthermore, ATPD studies with depletion levels of this magnitude have noted significant reductions in catecholamine metabolites (Palmour *et al*, 1998) and catecholamine synthesis (Jaskiw and Bongiovanni, 2004; McTavish *et al*, 1999a,b), and significant increases in plasma prolactin levels (an indirect measure of dopamine function) (Harmer *et al*, 2001). However, depletion of dopamine with ATPD in the present study resulted in no significant change in either PPI or P50 suppression. These findings are contrary to a number of reports showing evidence for dopaminergic modulation of PPI and P50 suppression in healthy human subjects. For example, the dopamine D₂ receptor agonist bromocriptine (Abduljawad *et al*, 1998, 1999), the D₁/D₂ agonist, pergolide (Bitsios *et al*, 2005), the D₃ agonist, ropinirole (Giakoumaki *et al*, 2007), and the dopamine reuptake inhibitor and releaser, amphetamine (Hutchison

and Swift, 1999; Light *et al*, 1999) and amantadine (Bitsios *et al*, 2005) have all been shown to reduce either PPI and/or P50 suppression. However our findings do support a number of other studies in healthy human subjects that have failed to find robust effects on PPI or P50. For example, studies have shown that augmenting dopamine neurotransmission with the dopamine agonists amphetamine, bromocriptine, pergolide, and L-dopa have no effects on PPI and P50 suppression (Kumari *et al*, 1998; Swerdlow *et al*, 2002a,b; Oranje *et al*, 2004).

Although the reasons for the inconsistency are not clear, it is possible that differences in sample characteristics as well as in dose and pharmacokinetics of the drugs may account for some of the discrepancies. Alternatively, as reported in animals (Martin-Iverson and Else, 2000; Swerdlow *et al*, 2001, 2002b,c) and as discussed for the serotonin section, inconsistencies may be related, in part, to differences in PPI stimulus parameters including lead intervals and their sensitivity to dopaminergic modulation. Furthermore, there is increasing evidence that the effects of dopaminergic drugs on PPI may be related to baseline PPI, with greater reductions reported in subjects with high baseline PPI (Bitsios *et al*, 2005; Giakoumaki *et al*, 2007). This may also be extended to P50 effects, as baseline P50 suppression differences have been reported according to differences in the functional allelic catechol-O-methyltransferase polymorphism with valine homozygous subjects exhibiting the greatest P50 suppression deficits (Lu *et al*, 2007).

Another critical factor that could explain the variability in the findings is a possible imbalance in dopamine neurotransmission (ie away from an optimal level) following dopaminergic modulation. Consistent with this assertion, one prominent hypothesis describes an inverted 'U'-shape representation of dopamine function within frontal networks (Arnsten and Goldman-Rakic, 1998; Goldman-Rakic, 1995). In this model there is a restricted range of DA stimulation for optimal prefrontal function, and any significant change in neurotransmission, that is, either too little stimulation (DA receptor blockade) or too much stimulation (such as that which occurs when exposed to stress) results in DA dropping out of the normal functioning range, and hence impairment of dopamine-dependent prefrontal functions (Arnsten and Goldman-Rakic, 1998). At the cellular level similar findings have also been observed, with prefrontal neurons also appearing to exhibit an inverted U response to D₁ receptor stimulation (Williams and Goldman-Rakic, 1995). In support of the importance of optimal dopamine stimulation in the regulation of gating, Moxon *et al* (2003a,b) have developed a computer model of dopaminergic modulation of the P50 ERP in the hippocampus, which can explain the relationships between sensory gating and dopaminergic function in schizophrenia. They found both excessive and reduced dopamine levels attenuated sensory gating responses by modulating the signal-to-noise ratio in the prefrontal cortex. Excessive dopamine increases the likelihood of neuronal firing causing the neurons to become hyper-responsive. In this state, cells in the neural circuits lose the ability to be activated synchronously by auditory stimuli. Given that synchronous activity is then not available to create large amplitude responses, the P50 amplitude is reduced.

Excessive activation of dopaminergic receptors can also result in an increase in the background amplitude of the EEG, such that when a P50 signal is produced to an auditory stimulus, it cannot be seen above the background level of noise. Similarly, reduced synchronous activity occurred when dopaminergic activity was very low, thus resulting in decreased P50 amplitudes.

In the current study, as selective depletion of dopamine had no effects on either measure of gating, we suggest that the amount of dopamine depletion achieved with ATPD was still within the range required for optimal performance. This is likely given that tyrosine/phenylalanine depletion is thought to be a mild challenge for the dopamine system, with studies showing relatively small changes on physiological and neurochemical measures of dopamine function. For example, tyrosine/phenylalanine depletion has been found to induce only a 6% increase in [11 C] raclopride binding, which may correspond to an approximate 10–20% reduction in dopamine concentrations (Montgomery *et al*, 2003). Additionally, it appears to induce only a modest increase in plasma prolactin levels (Harmer *et al*, 2001; Montgomery *et al*, 2003). Furthermore, modest or no effects of tyrosine depletion have been noted on dopamine-dependent cognitive processes, such as working memory (Ellis *et al*, 2007; Harmer *et al*, 2001; Harrison *et al*, 2004). Hence it is possible that our study on dopamine depletion, as well as that of others investigating the effects of dopamine agonists on PPI and/or P50 suppression (Kumari *et al*, 1998; Swerdlow *et al*, 2002a, b; Oranje *et al*, 2004), may have not caused significant changes in dopamine neurotransmission to the level required for disruption of either sensorimotor or sensory gating. The findings of an amphetamine-induced reduction in PPI only in smokers (Kumari *et al*, 1998) (ie causing larger increases in dopamine neurotransmission and pushing these subjects downward the putative inverted U curve) and the dopamine agonist-induced reduction in PPI in subjects with high baseline PPI (Bitsios *et al*, 2005) (ie causing larger increases in dopamine neurotransmission in subjects who may already have higher baseline dopamine and thus causing a similar downward shift in the inverted U curve), support the possibility that the relationship between dopamine neurotransmission and sensorimotor or sensory gating may follow an inverted U-type relationship.

In summary, our findings indicate no changes in PPI and P50 suppression following selective depletion of dopamine with ATPD, and support the findings of a number of studies using dopamine agonists. However, the effects of dopamine on PPI and P50 suppression may depend on the relative dopamine tone, with too much or too little dopamine neurotransmission impairing sensorimotor or sensory gating.

Combined Serotonin and Dopamine Depletion

CMD with acute tryptophan, tyrosine, and phenylalanine depletion induced an 86% reduction in the ratio of tryptophan to other LNAAs, together with a 90% decrease in the ratio of tyrosine to other LNAAs, and a 92% decrease in the ratio of phenylalanine to other LNAAs. These levels of depletion were not statistically different from the levels achieved under the selective depletion of tryptophan, or of

tyrosine/phenylalanine, indicating that all three monoamine precursors were depleted simultaneously to levels that are expected to affect central neurotransmitter function (Nathan *et al*, 2004). Interestingly, this simultaneous depletion of dopamine- and serotonin-induced reductions in both PPI and P50 suppression providing evidence that both serotonin and dopamine may act synergistically to modulate sensorimotor and sensory gating. These findings, together with the findings discussed above for selective serotonin and dopamine depletion could be interpreted in many ways. First, it is possible that both serotonin and dopamine may modulate both PPI and P50, but independently they require significant perturbation of each system to affect gating. Hence, factors discussed previously such as dose, potency, and an inverted U relationship may all play a significant role in the likelihood of changes to gating occurring when targeted selectively. Second, it is possible that when targeted simultaneously, there may be a synergistic interaction between the serotonin and dopamine systems such that more robust and more consistent effects on gating are observed. Such effects on PPI and P50 suppression have been noted with regard to the noradrenergic system and its interaction with the serotonin system. Inconsistent effects of selective augmentation of noradrenaline (with noradrenaline reuptake inhibitors) on PPI have been reported with no effects with reboxetine (Phillips *et al*, 2000b) and a reduction with the more potent desipramine (Oranje *et al*, 2004), whereas simultaneously augmenting serotonin and noradrenaline with imipramine (a tricyclic antidepressant drug that inhibits both serotonin and noradrenaline reuptake) impaired both PPI and P50 suppression (Hammer *et al*, 2007).

The reductions in both PPI and P50 suppression with simultaneous serotonin and dopamine depletion may be important for our understanding of the neurochemical basis of sensorimotor and sensory gating deficits in schizophrenia. Our finding, together with evidence that the PPI and P50 suppression reductions in patients with schizophrenia may be normalized with atypical antipsychotics, which target both serotonin and dopamine neurotransmission (ie by inhibiting dopamine D₂ receptors and 5-HT₂ receptors) (Hamm *et al*, 2001; Kumari and Sharma, 2002; Kumari *et al*, 2007; Light *et al*, 2000), suggests that dysfunction in both serotonin and dopamine neurotransmission may in part contribute to the disruption in sensorimotor and sensory gating observed in schizophrenia.

Although PPI and P50 suppression are both measures of gating, they are not correlated (Braff *et al*, 2007; Brenner *et al*, 2004; Oranje *et al*, 2006) and thus it has been suggested that they may not share the same neural mechanisms (Braff *et al*, 2007; Brenner *et al*, 2004). It is also possible then that there may be differential modulation of sensorimotor and sensory gating by various neurochemical systems (Braff *et al*, 2007). In our study, there was some evidence for differential effects of serotonin and dopamine on sensory vs sensorimotor gating, as selective depletion of serotonin had no effects on P50 suppression but disrupted PPI. However, our findings of reductions in both PPI and P50 suppression with simultaneous depletion of both serotonin and dopamine suggest that both sensorimotor and sensory gating may be modulated by similar neurochemical systems and these systems may work synergistically. This

supports the suggestion that while PPI and P50 do not share the same neural networks, they may share overlapping networks (Oranje *et al*, 2006) and hence it is possible that both serotonin and dopamine's modulation of PPI and P50 may be similar within critical areas of the overlapping network. These findings in general support observations in animals with equivalent measures on the neurochemical regulation of sensorimotor and sensory gating (Swerdlow *et al*, 2006).

There are some important methodological issues that require discussion here. First, the current study was conducted in males only. There is some evidence that the PPI levels are lower in females than in males (Swerdlow *et al*, 1993) and the 'female' sex steroid, estrogen, has been shown to attenuate PPI deficits (Gogos *et al*, 2006). Hence these findings cannot be extended to females. Second, given that we postulate the lack of effect of dopamine depletion on PPI and P50 suppression in the current study to be due to insufficient depletion of dopamine, it would be of interest to replicate this study using a pharmacological probe that can decrease dopaminergic function to a greater extent (ie α -methyl-para-tyrosine). It is also worth noting here that the lack of effects observed after ATPD, and lack of change in PPI after ATD, cannot be explained by lack of power. Our study was adequately powered to detect a moderate effect size. The nonsignificant results all had a very small effect size (partial η^2 was 0.2 and 0.013–0.18 for PPI and P50, respectively), suggesting that the effects were too small to be of physiological relevance. Finally, the findings of the current study are following acute pharmacological manipulation of the dopamine and serotonin systems in humans. The consequences of chronic dopamine and serotonin manipulation on PPI and P50 in humans require further investigation.

In summary, the current study investigated the effects of selective and simultaneous serotonin and dopamine depletion on PPI and P50 suppression measures of sensorimotor gating. The findings provide evidence for neurochemical differentiation with regard to the effects of serotonergic and dopaminergic modulation on PPI and P50 suppression. Selective depletion of dopamine had no significant effect on either PPI or P50 suppression, whereas selective serotonin depletion significantly disrupted PPI, but not P50 suppression. Finally, the simultaneous depletion of both dopamine and serotonin resulted in significant reductions in both PPI and P50 suppression. We suggest that these results can be explained by theories relating to optimal levels of neurotransmission and synergistic interactions between monoaminergic systems for normal 'gating' function. These findings suggest that a dysfunction in both serotonin and dopamine neurotransmission (eg disruption of optimal neurotransmission leading to dopaminergic hyperactivity in striatum or dopaminergic underactivity in cortex) may in part be responsible for the gating deficits observed in schizophrenia and that the effects of atypical antipsychotic drugs on sensorimotor gating and sensory gating may be related to normalization of optimal neurotransmission (ie reducing striatal dopaminergic hyperactivity and enhancing cortical dopaminergic underactivity). The recent evidence that atypical antipsychotic drugs including risperidone and olanzapine activate areas including the striatum and frontal cortex during PPI (Kumari *et al*, 2007) supports such a possibility.

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DISCLOSURE OF CONFLICT OF INTEREST

None of the authors have any financial interests to disclose.

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