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ORIGINAL INVESTIGATION

Effects of trifluoromethylphenylpiperazine (TFMPP) on interhemispheric communication

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Abstract
Background 'Party Pills' containing trifluoromethylphenylpiperazine (TFMPP) and benzylpiperazine are legally available in many countries and marketed as safe alternatives to other illicit substances such as methamphetamine and methylenedioxymethamphetamine (or Ecstasy). They have gained huge popularity around the world, especially amongst young adults. However, there is no information currently available describing the acute neurophysiological effects of these psychoactive drugs in humans. The purpose of this study is to investigate the effects of TFMPP on central information processing speed in humans.
Methods A randomised, double blind, placebo-controlled study using electroencephalography (EEG) was carried out to investigate the effects of TFMPP on interhemispheric transfer time (IHTT). Healthy, right-handed males (age: 25 ±5.6 years) were given placebo (n=15) or TFMPP (0.94 mg/kg, oral, n=15) and tested both pre- and 2 h post-drug administration. High-density EEG recordings (128 channels which were re-referenced using an average reference to make 129 electrodes) were used to record event-related potentials. The N160 component was defined as the biggest negative peak in the range between 140 and 220 ms after the event. The IHHTs were analysed by deducting the N160 latency obtained in the contralateral hemisphere from the N160 latency obtained in the hemisphere ipsilateral to stimulus signal.
Results Statistical analysis using a split-plot design analysis of variance revealed that TFMPP significantly reduced the IHTT but did not affect reaction time. No statistically significant changes were observed in the placebo group.
Conclusions This study is the first to report the neurophysiological effects of TFMPP in humans and suggests that TFMPP may affect transmitter systems involved in speeding of interhemispheric communication in the male brain.

Keywords Trifluoromethylphenylpiperazine · Central nervous system stimulants · Interhemispheric transfer · Electroencephalography · Event-related potentials · Humans

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Introduction

Products containing trifluoromethylphenylpiperazine (TFMPP) and/or benzylpiperazine (BZP) are available for recreational use in many parts of the world despite their illegal status in some countries. They are marketed as a safe and legal alternative to methylenedioxymethamphetamine (MDMA/Ecstasy) and other amphetamines. In New Zealand, since their introduction in 2000, Party Pills gained popularity especially amongst young adults, and it was reported that one in five people in New Zealand have tried Party Pills, 71% of these were aged between 18 and 24 years (Wilkins et al.

2006). Both BZP and TFMPP are now banned in many countries such as Australia, Japan and parts of Europe (Erowid 2008). The New Zealand government reclassified these substances under the Misuse of Drugs Act (1975) in April 2008, placing them in the same class as cannabis.

BZP shares a similar chemical structure with other amphetamines. The potentially addictive characteristics of BZP were identified when former amphetamine addicts rated BZP higher than dexamphetamine using a scale measuring subjective drug liking. In the same study, BZP (100 mg, oral) produced an increase in heart rate and blood pressure and subjective mood effects comparable to dexamphetamine (7.5–10 mg, oral) in humans (Campbell et al. 1973). These findings are supported by a recent study reporting that BZP (200 mg, oral) significantly increased blood pressure and heart rate in humans (Lee et al. 2008b; Lin et al. 2009). Furthermore, BZP significantly increased self-reported subjective feelings such as stimulated, euphoria, sociability and drug liking measured by Visual Analog Scales and the Profile of Mood States questionnaire (Lin et al. 2009).

TFMPP has long been used as a serotonergic agent in receptor binding and animal behavioural studies. The stimulus properties of TFMPP appear to be mediated by serotonin (5-HT_{1B}) and 5-HT_{2C} receptors in animal models (Glennon et al. 1988; Herndon et al. 1992; Schechter 1988). Similar to MDMA, TFMPP stimulates 5-HT transporter (SERT)—mediated 5-HT release from neurons both in vitro and in vivo (Auerbach et al. 1990; Baumann et al. 2005; Pettibone and Williams 1984). Studies have also reported rodents trained to discriminate fenfluramine and MDMA from saline generalised to TFMPP, supporting some abuse liability for this compound (Schechter 1988). Results from clinical trials suggest TFMPP has moderate stimulating actions in humans (Jan et al. 2010; Lee et al. 2008a). Interestingly, TFMPP was neither self-administered nor produced detectable amphetamine-like effects in rhesus monkeys (Fantegrossi et al. 2005).

It is well established that transfer of information between the hemispheres is crucial in many cognitive tasks (Hoptman and Davidson 1994) and that the presence of the corpus callosum (CC) is critical to hemispheric interaction and interhemispheric communication (Cherbuin and Brinkman 2006; Rugg et al. 1984; Tettamanti et al. 2002; Weber et al. 2005). Poffenberger investigated the interhemispheric transfer time (IHTT), stating that it refers to the time taken for transfer of information from one hemisphere to the other hemisphere via the CC, hence reflecting the speed of human information transfer (Poffenberger 1912). Our previous EEG work (Barnett and Kirk 2005; Barnett et al. 2005; Iwabuchi and Kirk 2009; Rolfe et al. 2007), and that of others (Brown et al. 1994; Jeeves and Moes 1996; Nowicka and Fersten 2001; Saron and Davidson 1989), have shown that IHTT from the right to the left hemisphere is shorter than that from left to right. It has been proposed, for example, that this is due to the right hemisphere having a greater number of fast-conducting corticocortical connections than the left hemisphere (Miller 1996). However, it also seems that it is only true for right-handed males. Left-handers (Iwabuchi and Kirk 2009), females (Nowicka and Fersten 2001) and musicians (Patston et al. 2007) show less asymmetry in IHTT direction. This fits with numerous reports of less lateralisation in these groups (Knecht et al. 2000; Potter and Graves 1988; Shaywitz et al. 1995). In addition, those with a variety of central nervous system (CNS) disorders (Barnett and Kirk 2005; Barnett et al. 2005; Burnison et al. 1995; Rolfe et al. 2007) differ from the general asymmetric IHTT pattern also.

Despite the apparent dysfunctions in IHTT within these CNS disorders, information about the underlying mechanism is sparse. Very few studies have been conducted to identify the relationship between the interhemispheric transmission and neuropharmacologically active compounds. IHTT has shown to be lengthened late in the menstrual cycle, an effect that is thought to be due to progesterone (Kirk et al. 2008), and alcohol consumption led to slower interhemispheric transmission times (Khan and Timney 2007). Here however, a behavioural reaction time (RT) measure was used for IHTT calculation that is less valid than that calculated using visual-evoked potentials (VEP; Saron et al. 2003). Also, a nootropic drug piracetam repeatedly produced faster interhemispheric communication in rats (Buresova and Bures 1976).

In order to understand the process of interhemispheric transfer via the CC, some researchers have suggested that each hemisphere can inhibit the other via the CC (Cook 1984). Interhemispheric inhibition is hypothesised to be mediated through excitatory callosal neurones, acting on local inhibitory gamma-aminobutyric acid (GABA) neurones (Chen 2004). Both $GABA_A$- and $GABA_B$-mediated influence on transcallosal responses have been reported in humans (Irlbacher et al. 2007). It has been reported that the $GABA_B$-agonist baclofen strengthened interhemispheric inhibition via postsynaptic $GABA_B$ receptors whereas the $GABA_A$-agonist midazolam caused attenuation of interhemispheric inhibition.

As detailed below, in the current study we use EEG during the Poffenberger paradigm to assess the effect of TFMPP on neural processing via measurement of interhemispheric transmission. EEG potentials such as the P300 are usually employed to investigate the effects of drugs (Ascioglu et al. 2004; Deslandes et al. 2004). However, we suggest that the EEG of the Poffenberger is a more direct measure of processing speed, and one that is less confounded by processes such as attention that may be themselves are affected by the drug. Psychostimulant drugs such as amphetamine, caffeine, cocaine and methylpheni-

date have been reported to improve the level of vigilance, attention and general cognitive performance (Koelega 1993). However, no studies investigated the effects of psychostimulants on interhemispheric transfer time. Therefore, it is hypothesised that TFMPP, a psychostimulant, will influence IHT on the Poffenberger task. To our knowledge, our study is the first of its kind to investigate the effects of the recreational drug TFMPP on the human information processing. Since humans who consumed TFMPP report changes in subjective mood, there are reasons to believe that TFMPP changes in neurodynamics in human brain.

Materials and methods

Participants

Thirty male participants (mean age: 25 years, SD=5.6) completed the study. They were recruited through word-of-mouth referrals and posters. Participants were excluded on the basis of a self-reported history of mental illness, cardiac disease, head trauma, excessive drug use and epilepsy. The Edinburgh Handedness Inventory was administered to ensure participants were predominantly right-handed (Oldfield 1971). Participants were considered right-handed if their laterality quotient (LQ) was 50 or greater. All participants had a strong right-hand preference (mean LQ of 84.4, SD= 18.4). All participants signed a written informed consent form. This study received an ethical approval from the Northern X Regional Ethics Committee of New Zealand (Ref NTX/06/04/032). Participants were remunerated for participation.

Drugs

TFMPP hydrochloride (1-(α,α,α-trifluoro-m-tolyl) piperazine, 98+% purity) was sourced from Sigma Aldrich (New Zealand). Its purity and structure were also confirmed by LCMS in our laboratories. TFMPP hydrochloride (60 mg) and placebo (Lactose) tablets were subsequently manufactured at the University of Auckland. Drugs were orally administered with 200 mL of water.

Procedure

Participants were asked to refrain from ingesting alcohol the night before, and breakfast and caffeinated drinks on the morning of the trial. They were checked for the exclusion criteria and completed the Edinburgh Handedness Inventory. A standard breakfast consisting of two pieces of toast, a choice of sugar-free spread and decaffeinated tea/coffee or water was offered. The study medication (placebo or TFMPP 60 mg) was given approximately 60 min following breakfast. Participants were then tested using EEG before and 2 h after receiving either TFMPP (n=15) or placebo (n=15).

Electroencephalogram acquisition

EEG experiments were carried out in an electrically shielded Faraday chamber that was dimly illuminated while the participants were monitored by two cameras mounted inside. EEG was continuously recorded (1,000 Hz sampling rate, analogue band-pass 0.1–400 Hz) using an Electro Geodesics Inc. 128-channel Ag/AgCl electrode net (Electrical Geodesics Inc., Eugene, Oregon, USA). The impedance of the electrodes ranged between 35 and 40 kΩ. Visual stimuli were presented on a SVGA monitor (640×480-pixel resolution) at a distance of 57 cm, which presented the stimuli at a visual angle of 4° to the left or right of the fixation cross. The stimuli were black- and white-chequered circles, which flashed on either the left visual field (LVF) or the right visual field (RVF) or both visual fields (BVF). The stimuli were presented for a duration of 92 ms, which was below the 150-ms threshold that would result in an eye saccade (Kalesynkas and Hallett 2002). Participants were instructed to focus on the fixation cross in the centre of the screen and respond as quickly as possible to the onset of the stimulus in any position by pressing the space bar on the keyboard. Four blocks of trials using the right hand (RH) and the left hand (LH) were presented in the following sequence in order to counterbalance; RH–LH–LH–RH, or LH–RH–RH–LH. The experiment was randomised with 120 trials presented in the LVF, 120 in the RVF and 120 trials in the BVF. In each trial, EEG recording started 100 ms before the presentation of stimulus and lasted 600 ms.

Data analysis

The EEG data were segmented and analysed using in-house programmes. EEG segments contaminated by eye blinks (rejection criterion of 70 μV in eye channels) were rejected and automatic eye-movement correction was conducted (Jervis et al. 1985). The data was separated by three visual fields; LVF, RVF or BVF. Recordings of each participant were segmented into epochs with a pre-stimulus baseline of 100 ms and a post-stimulus period of 500 ms, which were then averaged for two visual fields; LVF and RVF (Iwabuchi and Kirk 2009). IHTT was measured using the VEP. Ten electrodes in the central–parietal area were used to calculate IHTT. The EEG recordings were band-pass filtered using a bidirectional three-pole Butterworth filter between 0.1 and 40 Hz (Alarcon et al. 2000). The visual-evoked N160 latency has been identified as a reliable measure of callosal transfer time (Nowicka and Fersten 2001). The N160 component was defined as the biggest

negative peak in the range 140–250 ms after stimulus onset and easily identified in each participant's recording. The IHHTs were analysed by subtracting the N160 latency obtained in the contralateral hemisphere from the N160 latency obtained in the hemisphere ipsilateral to stimulus signal (see Fig. 1). Mean RTs for all participants were obtained using E-Prime (Psychology Software Tools) programme. The absolute N160 latency, the IHTT and RT were examined using the Statistical Package for the Social Sciences Version 15.0 (SPSS Inc., Chicago, Illinois, USA). For N160 latency, a 2×2×2×2 split-plot ANOVA (SPANOVA) was performed, with hemisphere (left, right), time (before, after) and visual field (left, right) as the within-participants factors and treatment (TFMPP, placebo) as the between-participants factor. For IHTT, a 2×2×2 SPANOVA was performed, with transfer direction (LH-to-RH, RH-to-LH) and time (before, after) as the within-participants factors and treatment (TFMPP, placebo) as the between-participants factor. For RT, a 2×2 ANOVA was performed, with time (before, after) as the within-participants factor and treatment (TFMPP, placebo) as the between-participants factor.

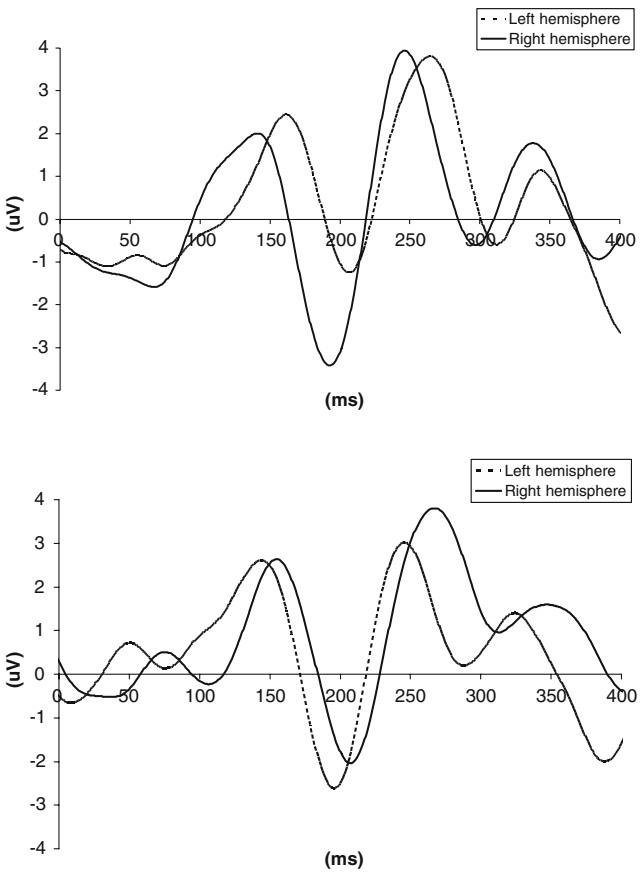

Fig. 1 Visual-evoked potentials (VEP) of a right-handed participant for the LVF (*top*) stimulation and RVF (*bottom*) stimulation conditions. The interhemispheric transfer time was determined by subtracting the N160 latency in the contralateral hemisphere from the N160 latency in the hemisphere ipsilateral to a visual stimulus

Results

N160 latency

Following the administration of TFMPP, there was a significant main effect of hemisphere ($F_{(1,28)}$=63.225, p<0.001) and time ($F_{(1,28)}$=13.709, p<0.001). A significant interaction between the time×treatment ($F_{(1,28)}$=7.088, p<0.05) indicates that TFMPP reduced N160 latency. In addition, significant interactions were observed between hemisphere×visual field ($F_{(1,28)}$=860.762, p<0.001), hemisphere×time×visual field ($F_{(1,28)}$=34.705, p<0.001), and hemisphere×time×visual field×treatment ($F_{(1,29)}$=9.617, p<0.005). The statistical significance of the hemisphere×visual field interaction indicated that the N160 latency in the directly stimulated hemisphere (contralateral hemisphere to visual stimulus) was shorter than the latency of the indirectly stimulated hemisphere (ipsilateral hemisphere to visual stimulus). This type of interaction is regarded as an indicator of interhemispheric transfer of information through transcallosal commissures (Endrass et al. 2002; Nowicka and Fersten 2001).

Interhemispheric transfer time

There was a significant main effect of time ($F_{(1,28)}$=34.705, p<0.001) and hemisphere ($F_{(1,28)}$=63.225, p<0.001). In addition, there was a significant interaction between the time and treatment ($F_{(1,28)}$=9.617, p<0.005), indicating that TFMPP reduced the IHTT. In agreement with our previous EEG work in right-handed males (Barnett and Kirk 2005; Barnett et al. 2005; Iwabuchi and Kirk 2009; Rolfe et al. 2007), these results show shorter IHTT from the right to the left hemisphere compared to left to the right hemisphere in both TFMPP and placebo groups (see Fig. 2a and b). Following TFMPP administration (Fig. 2a), the IHTT was shortened in both directions (i.e. Right–left and Left–right). The IHTT in the placebo group did not show significant changes (Fig. 2b). The interaction between hemisphere×time×treatment was not significant, suggesting TFMPP did not preferentially influence one hemisphere over the other.

Reaction time

There was a significant main effect of time ($F_{(1,28)}$=20.861, p<0.001), but no significant interaction between time×treatment ($F_{(1,28)}$=1.059, p>0.05). Therefore, TFMPP administration did not affect reaction time. However, a trend of reduced mean RTs were observed for both groups (Fig. 3).

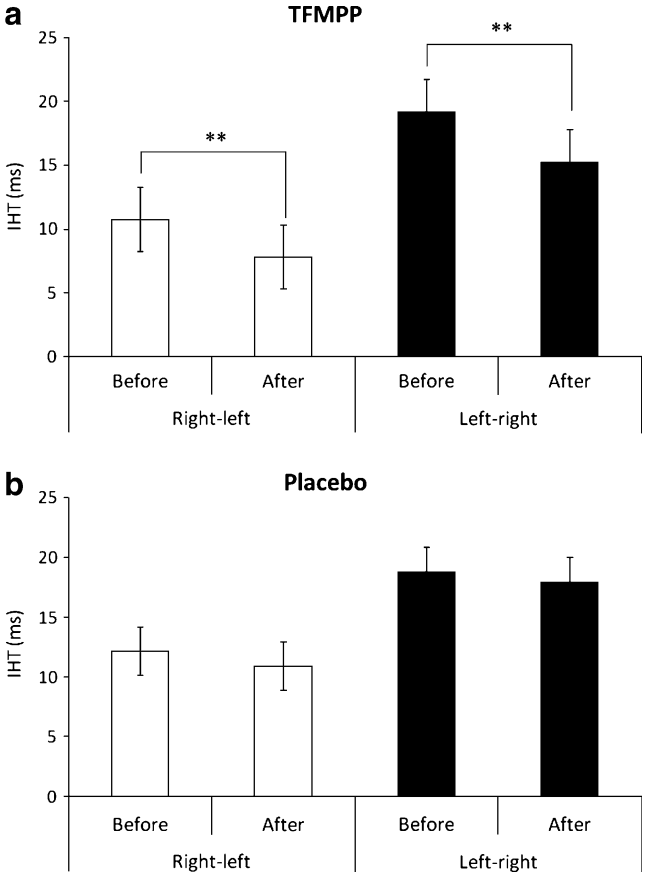

Fig. 2 **a** IHTT of TFMPP group significantly reduced in both directions; right-to-left ($F_{(1,28)}$=63.225, p<0.001) and left-to-right ($F_{(1,28)}$=63.225, p<0.001). *Vertical bars* represent standard error of the mean. **b** Interhemispheric transfer time did not change significantly following placebo. *Vertical bars* represent standard error of the mean

Discussion

The present study was designed to measure the speed of visual information transfer between two hemispheres following TFMPP in male subjects. In agreement with previous work, we found that overall, IHTT from the right to the left hemisphere was faster than that from the left to the right (Barnett and Kirk 2005; Barnett et al. 2005; Brown et al. 1994; Iwabuchi and Kirk 2009; Jeeves and Moes 1996; Nowicka and Fersten 2001; Rolfe et al. 2007; Saron and Davidson 1989), confirming the asymmetry of speed of callosal communication in right-handed males. However, for the first time we have shown that TFMPP significantly shortened the IHTT in both directions (LH to RH, RH to LH), without affecting the reaction time. This effect was not observed in the placebo group, indicating that pharmacological effects of TFMPP were responsible for this. Although we observed significant speeding of RT before and after, lack of significant interaction between time×treatment ($F_{(1,28)}$=1.059, p>0.05) indicates TFMPP did not influence the RT. Therefore we suggest the significant main effect of time was due to a practice effect, and the physiological changes we observed (EEG data) are independent of behavioural effects (RT data). Similarly, the discrepancies between electrophysiological and behavioural results have previously been reported in human subjects (Potter et al. 1992; Rugg and Nagy 1989; Smith and Halgren 1989). Behavioural measures are sometimes unable to detect the effects of psychostimulants on cognitive function because of their relative insensitivity; consequently, a large number of trials and participants are often needed to obtain reliable data. It is possible that our RT task was insufficiently powered to enable the determination of significant changes with a small number of participants. According to Saron and Davidson (1989), 'RT differences between conditions may be obtained as a function of a change in the overall state of the brain from one condition to the next rather than being associated specifically with interhemispheric transfer' (Saron and Davidson 1989). In addition, mean RT is influenced by speed of motor response (i.e. speed of access from the visual field of one hemisphere to the motor centre of responding hand) and whether callosal axons are myelinated or unmyelinated (Marzi et al. 1991; Saron and Davidson 1989). Therefore, the lack of a significant change in the mean RT data suggests that the VEP-ERP method provides direct and more sensitive information about treatment-related changes in the speed of interhemispheric transfer of information.

Many studies have investigated the nature of the interhemispheric communication via the CC, however, it has been difficult to identify the neurotransmitters involved in the process. It has been suggested that glutamatergic hypofunction may be responsible for disrupted interhemispheric communication in individuals with autism (Carlsson 1998; Nyden et al. 2004). This theory was suggested after

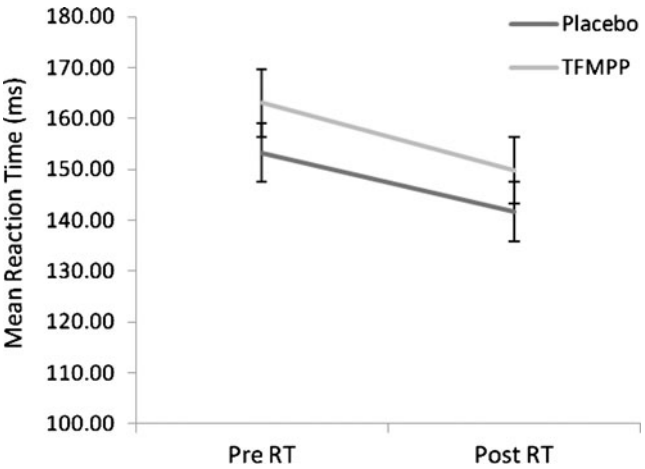

Fig. 3 Mean RT for placebo and TFMPP groups. *Vertical bars* represent standard error of the mean

observing similarities between the symptoms produced by *N*-methyl-*D*-aspartate (NMDA) antagonist treatment and symptoms of autism (Carlsson 1998). Furthermore, an electrophysiological study reported that minimal stimulation of the callosum evoked an NMDA receptor-mediated monosynaptic excitatory postsynaptic current (EPSP) in pyramidal neurons (Kumar and Huguenard 2001). The cells of neocortical callosal projections are almost exclusively pyramidal cells with excitatory asymmetric synapses on spines of pyramidal neurons in homo- and heterotopic regions of the contralateral cortex (Akers and Killackey 1978; Jacobson 1965; Jacobson and Trojanowski 1974; Wise and Jones 1976). Callosal projections are purely excitatory and it is reported the CC uses glutamate as its neurotransmitter (Aram and Lodge 1988; Kumar and Huguenard 2001).

Interestingly, 5-HT_{2A} receptor agonists like LSD, mescaline and psilocybin emulated symptoms of autism in the aforementioned trial (Carlsson 1998). From these reports, it is reasonable to hypothesise that both glutamate and serotonin neurons are involved in the callosal interhemispheric communication. The 5-HT_{2A} agonist LSD is thought to exert psychotogenic effects by stimulating GABAergic interneurons in the limbic cortex, thus reducing corticostriatal glutamatergic tone (Gellman and Aghajanian 1991). TFMPP, possessing some activity at 5-HT_{2A} receptors, may likewise induce hypoglutamatergia leading to aberrations of serotonergic activity in the cortex (Alhaider et al. 1993; Titeler et al. 1987). Serotonin neurons, along with dopaminergic and noradrenergic neurons, seem to be greatly modulated by corticofugal glutamatergic neurons either directly or via GABAergic interneurons, acting as 'accelerators' and 'brakes', respectively (Carlsson et al. 1999). The 'accelerator/brake' hypothesis suggests that when 5-HT is increased following administration of a stimulant such as TFMPP, there is a negative feedback loop where glutamatergic neurons indirectly inhibit the 5-HT release pathway through the inhibitory neurotransmitter GABA. Pyramidal cells co-express 5-HT_{1A} and 5-HT_{2A} receptors, and TFMPP has modest binding affinity for 5-HT_1 and 5-HT_2 receptor subtypes (Martin-Ruiz et al. 2001; Schoeffter and Hoyer 1989). Therefore, it is feasible to suggest that TFMPP has disconcerting influence on the balance between excitatory and inhibitory inputs therefore leading to an increased callosal activity that may shorten the IHTT.

Similar to MDMA, TFMPP also has an indirect effect on dopamine (DA) through actions on 5-HT receptors stimulation and GABA receptor blockade effectively increasing DA release in the ventral tegmental area (Nissbrandt et al. 1992). Furthermore, studies using positron emission tomography reported the involvement of the 5-HT_{1A} receptor in dopaminergic cell activity in caudate, putamen and mesolimbic pathway (Bantick et al. 2005), and 5-HT_2 receptors seem to increase the tonic release of DA in the nucleus accumbens and mesolimbic pathway, through an interaction with GABA (Devaud and Hollingsworth 1991; Parsons et al. 1999). >Both 5-HT_{1A} and 5-HT_{1B} receptors have been implicated in exerting stimulatory effects on mesocortical and prefrontal DA release (Hagino and Watanabe 2002; Morrow et al. 1999). Moreover, evidence 5-HT's modulation of cortical dopamine (Di Pietro and Seamans 2007; Fink and Gothert 2007; Pehek et al. 2006). Combining the evidence presented above, it is possible the changes observed in the IHTT are caused by TFMPP effects which are mediated via glutamatergic, serotonergic, gabaergic and dopaminergic pathways.

Anecdotal reports suggest TFMPP is capable of causing unpleasant side effects (Erowid Piperazines Vault 2007). However, in many cases, TFMPP was consumed in combination with other recreational drugs such as alcohol, tobacco, caffeine and other illicit drugs such as MDMA, methamphetamine and marijuana. Therefore, it is difficult to correlate negative side effects to TFMPP alone. We carefully monitored our participants for signs and symptoms of side effects during the course of the trial and the day after the trial, but none of our participants reported any unwanted side effects. Also, due to reasonably small dose of TFMPP administered, its effects were not very obvious to the observer and in most of participants. Consequently, the experimenters remained blinded until the end of the test period.

In summary, the present study has demonstrated, first, the sensitivity of our modified Poffenberger paradigm for measuring drug-induced effects on human information processing and, second, the ability of TFMPP to enhance the interhemispheric transfer of information via the CC. Our research suggests that studying the effects of recreational drugs on the human interhemispheric information processing would lead to an improved understanding of their mechanisms of action.

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