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ORIGINAL INVESTIGATION

Investigation of the effects of 'piperazine-containing party pills' and dexamphetamine on interhemispheric communication using electroencephalography

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Abstract
Background 'Piperazine-containing party pills' were marketed and sold as legal alternatives to methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) until 2008 in New Zealand. The major constituents of these 'pills' were benzylphenylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP). Despite their popularity, there is a paucity of knowledge about their central effects in humans. This study investigated their effects on human neural processing using electroencephalographic techniques.
Methods A randomised, double-blind, placebo-controlled study investigated the effects of an acute dose of these compounds on the interhemispheric transfer of information (IHTT) using the Poffenberger task. Reaction time data were also collected. Healthy, right-handed males were given an oral dose of either BZP ($n = 13$) (200 mg), TFMPP ($n = 15$) (60 mg), a combination of BZP + TFMPP ($n = 15$) (100 mg/30 mg), dexamphetamine ($n = 16$) (20 mg), or placebo ($n = 23$) and tested both before and 120 min after drug administration.
Results A mixed factorial repeated measures analysis of variance of absolute N160 latency and contrast analysis revealed that only TFMPP ($F_{(1,77)} = 17.30$, $p \leq 0.001$) significantly reduced the absolute N160 latency. Analysis of the IHTT revealed that only TFMPP ($F_{(1,77)} = 5.266$, $p \leq 0.02$) significantly reduced the IHTT, while BZP, BZP + TFMPP and dexamphetamine had no effect. Contrast analysis revealed that both TFMPP ($F_{(1,77)} = 17.30$, $p \leq 0.001$) and placebo ($F_{(1,77)} = 15.08$, $p \leq 0.001$) preserved the laterality of information transfer from one hemisphere to the other. Reaction time ($p > 0.05$) was not significantly affected by any of the drug treatments.
Conclusions The usual directional asymmetry (i.e. faster R-to-L transfer relative to L-to-R) observed in healthy control group was absent following the administration of either BZP, BZP + TFMPP or dexamphetamine. Surprisingly, lateralised hemispheric function was not affected by TFMPP. Our findings highlight how the administration of BZP, TFMPP and BZP + TFMPP leads to changes in the pattern of information transfer.

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

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Introduction

Products containing 1-benzylpiperazine (BZP) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP) were, until 2008, widely available for recreational use around the world. Animal studies report that BZP predominantly affects

dopamine (DA) and to a lesser extent, noradrenaline (NA) suggesting that BZP stimulates the monoamines modulated by drugs of abuse such as dexamphetamine, cocaine and MDMA and, hence shares similar abuse and dependence potential (Koob and Volkow 2010). Two human studies, both carried out in the early 1970s, reported BZP caused dexamphetamine-like effects such as increased blood pressure and heart rate and improved the performance of an auditory vigilance test (Bye et al. 1973; Campbell et al. 1973). In addition, BZP caused subjective effects comparable to dexamphetamine (Campbell et al. 1973). We also found that BZP produced dexamphetamine-like mood changes such as feelings of euphoria, of being 'high' and decreased fatigue (Lin et al. 2011). In contrast, TFMPP has been extensively used as a marker for 5-HT activity as it possesses wide range of affinity for 5-HT subtypes (Herndon et al. 1992). TFMPP is a substrate for the 5-HT transporter (SERT) and a releaser of 5-HT (Auerbach et al. 1990). Animal studies suggest the effects of TFMPP are exerted via 5-$HT_{1B/2C}$ receptors (Baumann et al. 2004; Hoyer and Schoeffter 1988), and it possesses MDMA-like hallucinogen and abuse potential (Yarosh et al. 2007). In our laboratory, the activities of TFMPP have been characterised in humans; participants reported increased dysphoria, as well as dexamphetamine-like effects, including increased tension/anxiety, drug liking and a feeling of being 'high'. These experiences were reported as comparable to those produced by LSD and MDMA.

The users of party pills frequently consumed a combination of BZP and TFMPP in order to mimic the amphetamine- and MDMA-like subjective experience (de Boer et al. 2001). When BZP and TFMPP are administered together, they produce synergistic effects in animals, compared to when they are given separately (Baumann et al. 2004, 2005). It has been suggested that BZP and TFMPP administered at a 1:1 ratio produce dramatic dose-related MDMA-like increases in dialysate 5-HT and DA, which provide supporting evidence for the combinations' popularity among recreational drug takers (Baumann et al. 2005). A recent study of humans carried out in our laboratory found that the combination of BZP + TFMPP increased blood pressure and heart rate and produced amphetamine-like subjective effects such as increased vigour, self-confidence and drug liking (Lin et al. 2011).

Despite reported similarities between BZP, TFMPP and psychostimulants such as amphetamine, research on the acute effects of these drugs on human cognition is limited. Previously, we investigated the effects of TFMPP on the interhemispheric transfer time (IHTT) and found that TFMPP significantly shortened the IHTT either from left to right hemisphere (LH-RH) or right to left hemisphere (RH-LH) (Lee et al. 2011), suggesting a drug-related effect on human information processing. Consistently, in our recent study investigating the differences in inhibition and selective attention following a single dose of BZP or TFMPP and the combination of BZP and TFMPP using an event-related Stroop functional magnetic resonance imaging (fMRI) paradigm, we found an increase in activation of the dorsal striatum following BZP and the thalamus following TFMPP (Curley et al. 2015). When BZP and TFMPP were administered together, both the dorsal striatum and thalamus were activated.

BZP has also been directly compared to dexamphetamine for its effects on selective attention and inhibition using fMRI and the Stroop task. The study found that BZP caused an increase in activity in the inferior frontal gyrus (IFG) and a decrease in the anterior cingulate cortex. In contrast, dexamphetamine reduced activity in IFG activity and increases it in thalamus (Curley et al. 2016). We have also shown that a single oral dose of either BZP or TFMPP, but not the combination of BZP/TFMPP, affected the auditory sensory-evoked P300 potential in a manner similar to dexamphetamine (Lee et al. 2015).

This current study aimed to further differentiate the effects of acute administration of BZP, TFMPP and the combination of BZP + TFMPP in comparison to dexamphetamine on the speed of visual information transfer between two hemispheres using event-related potentials (ERPs) during the Poffenberger paradigm. It is well known that information transfer between the hemispheres is crucial in many cognitive tasks and that ERPs provide a direct measure of neural processing (Hoptman and Davidson 1994). Animal studies have shown that rats circle strongly in one direction following injection of dopaminergic drugs (Glick and Hinds 1985; Jerussi and Glick 1976), suggesting a link between neurotransmitter systems and brain functional asymmetries (Glick et al. 1982). In humans, those with a variety of central nervous system (CNS) disorders, such as schizophrenia (Endrass et al. 2002), attention-deficit/hyperactivity disorder (ADHD) (Brown and Vickers 2004) and multiple sclerosis (Burnison et al. 1995) differ from the general asymmetric IHTT pattern. Given the stimulant-like effects of BZP, TFMPP and their combination, and their observed differences on cognition, we hypothesised that BZP and TFMPP would induce similar effects on IHTT as those induced by dexamphetamine, but their effects in combination on IHTT would be minimal. Like our previous study using TFMPP (Lee et al. 2011), we recorded the N160 component which has been used previously to estimate IHTT during the Poffenberger paradigm (Westerhausen et al. 2006) which is considered a reliable measure of interhemispheric transmission (Brown and Jeeves 1993).

Methods

Participants

This study received ethics approval from the Northern X Regional Ethics Committee of New Zealand. Healthy

right-handed male volunteers were recruited through university newspaper advertisements, posters and by word of mouth. Participants were selected using strict inclusion/exclusion criteria to minimise factors that could potentially influence an event-related potential (ERP) study of humans. The inclusion criteria were: physically healthy right-handed males, non-smokers, no regular prescription drugs and no past self-reported history of alcohol or other drug dependence. Participants were excluded on the basis of a history of mental illness, cardiac disease, head trauma, epilepsy or endocrine disorder. Females who were not recruited as human ERPs are reportedly affected by gender due to hormonal changes during the menstrual cycle (Hausmann et al. 2013). The Edinburgh Handedness Inventory was administered to ensure participants were predominantly right-handed (Oldfield 1971); participants were considered right-handed if their laterality quotient was 50 or greater.

Study design and procedure

The study was a randomised, placebo-controlled, double-blind experiment, where the participants were randomly allocated to one or another drug group. Written consent was obtained from all participants before enrolment in the study. Testing sessions began at 8 a.m. or 9 a.m. for each participant, and participants were asked to abstain from consuming alcohol for 24 h and caffeine for 12 h prior to the study. As ERPs are affected by circadian rhythms (Polich and Kok 1995), a maximum of two participants per day were examined and both were tested in the morning. A standard breakfast consisting of two pieces of toast, a choice of sugar-free spread and decaffeinated tea/coffee or water was provided to minimise the possible confounding effect associated with food intake on ERPs (Polich and Kok 1995). The participants (aged 18–39 years, with a mean age of 22.74 ± 4.22 years) were then randomly assigned to a drug group as follows: BZP ($n = 13$) (200 mg; Sigma-Aldrich), TFMPP ($n = 15$) (60 mg; Sigma-Aldrich), a combination of BZP + TFMPP ($n = 15$) (100/30 mg, Sigma-Aldrich), dexamphetamine ($n = 16$) (20 mg, Douglas Pharma ceuticals) or placebo ($n = 23$) (methylcrystalline cellulose, Sigma-Aldrich). Placebo capsules and those containing BZP, TFMPP and the combination BZP and TFMPP were manufactured by the School of Pharmacy, University of Auckland. All capsules were identical in appearance and administered with 200 mL of water. The doses of BZP and TFMPP were selected because they reflected the doses commonly consumed by drug users (Wilkins and Sweetsur 2010). We used lower doses in the combination of BZP and TFMPP due to the reported drug-drug synergism in animal studies (Baumann et al. 2004, 2005). The ERP testing was carried out prior to drug administration and again 120 min following drug administration allowing the drugs to reach their expected peak plasma concentrations (Lin et al. 2011). Participants were reimbursed with either movie or petrol vouchers. The participants were contacted the following day to enquire whether there were any drug-induced adverse effects.

EEG acquisition

EEG was recorded in an electrically shielded, sound-attenuated Faraday room dimly illuminated using DC-powered lighting. Participants were monitored by two closed circuit cameras mounted inside the chamber. EEG was continuously recorded (1000 Hz sampling rate, 0.1–400 Hz analogue band-pass) using an Electro Geodesics Inc. 128-channel Ag/AgCl electrode net. The impedance of the electrodes ranged between 35 and 40 kΩ. EEG was acquired using a common vertex (Cz) reference, but was subsequently re-referenced to an average of all electrodes.

Visual stimuli were presented on a SVGA monitor (640 × 480 pixel resolution) at a distance of 57 cm from the participant's eyes, which presented the stimuli at a visual angle of 4° to the left or right of a fixation cross located in the centre of the screen. The stimuli were black-and-white chequered circles, which flashed in either the left visual field (LVF) or the right visual field (RVF) with a variable interstimulus interval (550, 750 or 950 ms). 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 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 to the left visual field and 120 to the right visual field. Reaction time (RT) was also recorded to stimuli presented.

The EEG data were segmented and analysed using MATLAB-based in-house programmes. Those contaminated by eye movement (blink threshold set at 70 μV in eye channels) were discarded, and then visual inspection and automatic eye-movement correction (Jervis et al. 1985) was applied for eye movements and blinks. 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 or RVF. EEG recordings were band-pass filtered using a bidirectional three-pole

Butterworth filter between 0.1 and 40 Hz (Alarcon et al. 2000).

Statistical analysis

Group differences in RT were analysed using ANOVA, with time (pre, post) as the within-participants factor and drug (BZP, TFMPP, BZP + TFMPP, dexamphetamine, placebo) as the between-participants factor.

The N160 components were visually determined as the greatest negative peak between 140 and 250 ms after stimulus onset and were acquired separately for each participant. The absolute N160 latency was the latency between stimulus presentation and the N160 appearance at occipital electrodes, while the amplitude of N160 was the amplitude between the N160 and the previous positive peak. Five parietal electrodes (Fig. 1) on either side of the head (PO3, PO4, P3, P4, P5, P6, P7, P8, PO7, PO8) were chosen and averaged for analysis as these had been shown to produce the best statistical differences in N160 latency (Rugg et al. 1984). The IHTT was calculated by subtracting the peak N160 latency obtained in the ipsilateral hemisphere from the peak N160 latency obtained in the hemisphere contralateral to a visual stimulus which is considered the most accurate measure of visual-evoked potentials (Rugg et al. 1984). Figure 2 represents the visual-evoked potential of a right-handed participant for (a) LVF and (b) RVF stimulations. When the visual stimulus is presented to the LVF, it is registered first in the contralateral visual field (in the right hemisphere; red line), followed by the ipsilateral visual field (in the left hemisphere; blue line). Similarly, when the visual stimulus is presented to the RVF, it is registered first in the contralateral visual field (in the left hemisphere; blue line), followed by the ipsilateral visual field (in the right hemisphere; red line).

Differences in N160 latency were assessed using a mixed factorial ANOVA, with hemisphere (left, right), time (pre, post) and visual field (LVF, RVF) as within-participants factors and drug (BZP, TFMPP, BZP + TFMPP, dexamphetamine, placebo) as the between-participants factor. Differences in IHTT were subject to the same statistical analysis, with hemispheric transfer direction (left-to-right, right-to-left), and time (pre, post) as within-participants factors and drug (BZP, TFMPP, BZP + TFMPP, dexamphetamine, placebo) as the between-participants factor. A two-tailed level of significance was set to $p < 0.05$. All tests were carried out using the Statistical Package for the Social Sciences Version 15.0 (SPSS Inc., Chicago, IL, USA). Given the unequal sample sizes of each group, we ensured that the assumption of equality of variance was not violated due to unequal sample size and that the analysis was subject to a homogeneity test using SPSS.

Results

Reaction time (RT)

There was a significant main effect of RT ($F_{(1,77)} = 39.350$, $p \leq 0.001$). RT did not differ between groups at the baseline during pre-drug state; however, all groups showed a reduced RT after drug treatment, although this was not significant (Fig. 3). There were no significant interactions between time × drug ($p > 0.05$), implying that RT was not affected by drug treatment.

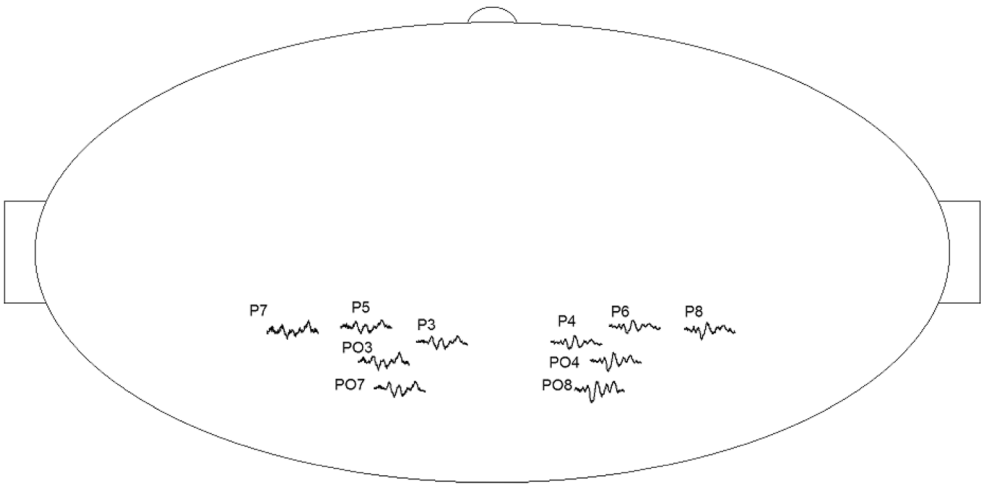

Fig. 1 Location of electrodes in N160 analysis

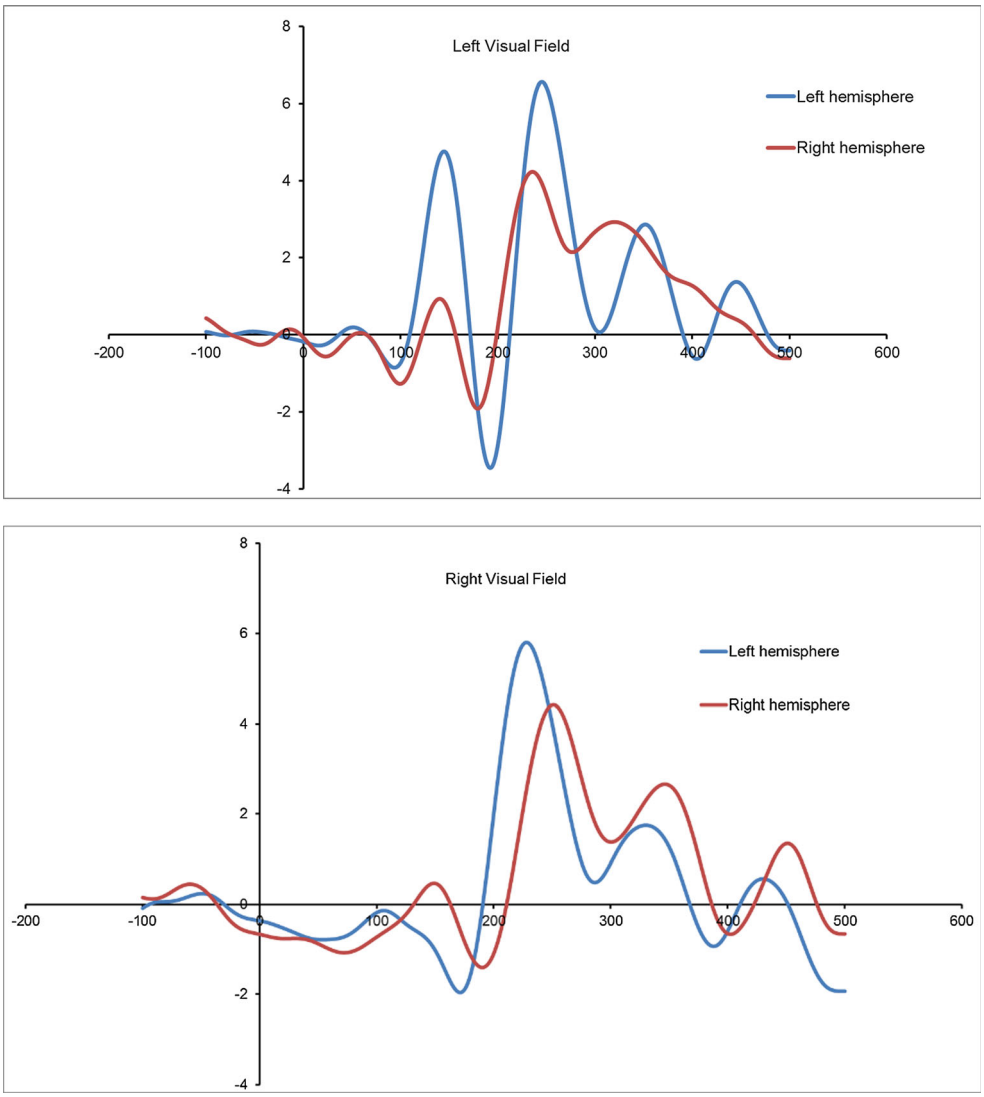

Fig. 2 Example of a visual-evoked potential of a right-handed participant for the left visual field stimulation and the right visual field stimulation conditions

N160 latency

There was a significant hemisphere × VF effect ($F_{(1,77)} = 657.98$, $p \leq 0.001$), indicating the occurrence of interhemispheric transfer of information through transcallosal commissures (Endrass et al. 2002). The time × drug interaction ($F_{(4,77)} = 5.007$, $p \leq 0.001$) was also significant indicating that N160 latency changed after drug treatment. Nevertheless, contrast analysis revealed that only TFMPP ($t = 17.30$, $p \leq 0.001$) significantly reduced the absolute N160 latency after drug administration, whereas BZP, BZP + TFMPP, dexamphetamine and placebo had no effect (Fig. 4).

Interhemispheric transfer time

The speed of Information transfer between hemispheres was assessed by determining the IHTT using the N160 latency difference between ipsilateral and contralateral hemispheres. There was a significant effect of hemispheric transfer direction ($F_{(1,77)} = 20.484$, $p \leq 0.001$), suggesting that the IHTT was faster when going from right-to-left compared to left-to-right. This is in agreement with previous research carried out in right-handed males (Barnett and Corballis). The time effect ($F_{(1,77)} = 7.60$, $p = 0.007$) was also significant which suggests there was a significant group difference in IHTT after drug treatment. In addition, there was a significant hemispheric transfer direction × drug interaction ($F_{(4,77)} = 2.902$, $p \leq 0.027$) which indicates that drug treatment affected interhemispheric transfer time in both directions. However, the hemispheric transfer direction × drug × time interaction was not significant which implies there was no significant drug effect in the IHTT contrast between pre- and post-treatment. Taken together, our results show that group differences in IHTT were primarily observed post-treatment.

Furthermore, two separate contrast analyses were carried out: the first tested whether each drug preserved the

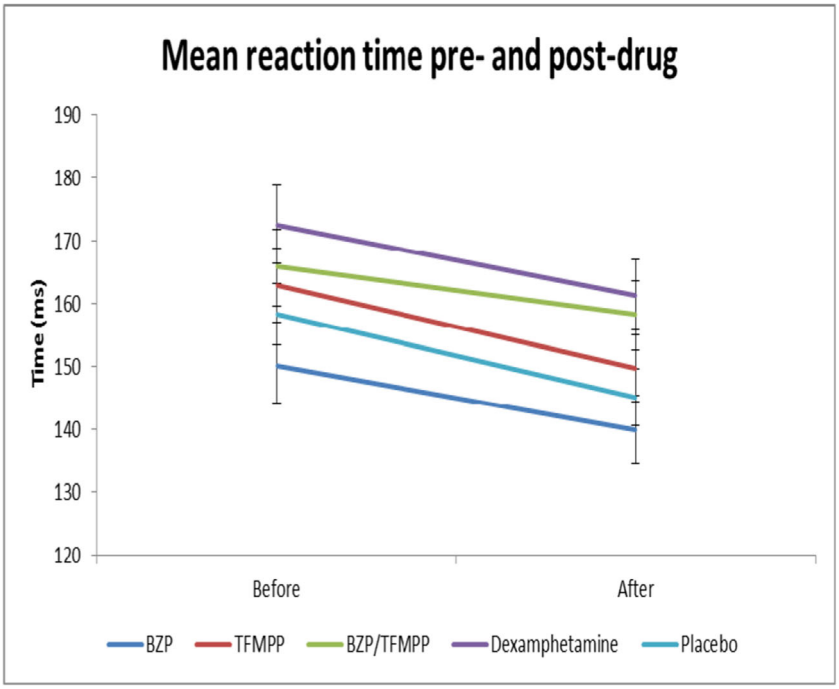

Fig. 3 Mean reaction time pre- and post-drug. *Error bars* represent standard errors of the mean

asymmetry of directional transfer and the second tested whether each drug had significant effects on IHTT. These analyses revealed that only TFMPP ($t = 17.30$, $p \leq 0.001$) significantly reduced the absolute N160 latency in both directions (i.e. right-to-left and left-to-right) after treatment, whereas the groups given either BZP, BZP + TFMPP, dexamphetamine or placebo did not significantly change the absolute N160 latency post-treatment (Fig. 4). Nevertheless, the normal interhemispheric asymmetry (i.e. faster right-to-left vs. left-to-right) was retained after either placebo ($t = 5.26$, $p \leq 0.001$, $d = 1.22$) or TFMPP ($t = 3.25$, $p \leq 0.001$, $d = 0.83$). Those given BZP ($t = -0.217$, $p = 0.83$, $d = 0.24$), BZP + TFMPP ($t = 0.39$, $p = 0.70$, $d = 0.05$) or dexamphetamine ($t = 0.90$, $p = 0.39$, $d = 0.10$) showed no significant differences in either direction (Fig. 5). Although, there was a trend towards increasing the speed of IHTT from right to left in those given BZP, BZP + TFMPP or dexamphetamine.

Discussion

The present study was designed to investigate the effects of BZP, TFMPP and BZP + TFMPP on the speed of visual information transfer between the two hemispheres relative to dexamphetamine and placebo. Consistent with previous studies of IHTT using ERP measures (Rugg et al. 1984), we found faster transfer times from the right to the left hemisphere than

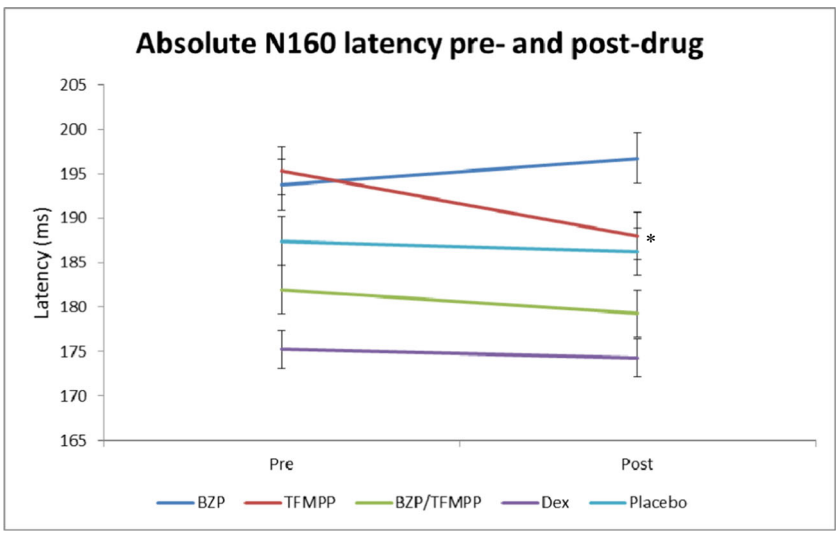

Fig. 4 Absolute N160 latency pre- and post-drug. *Error bars* represent standard errors of the mean (*$p < 0.05$)

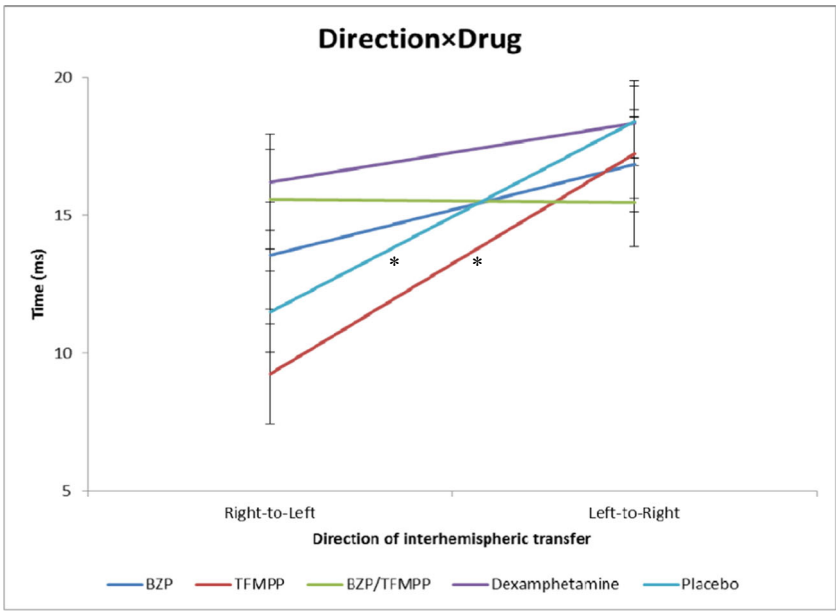

Fig. 5 Interhemispheric transfer time in each direction for drug group. *Error bars* represent standard errors of the mean (*$p < 0.05$)

from left to right in neurologically healthy adults. However, this usual directional asymmetry (i.e. faster R-to-L transfer) was absent following the administration of BZP, BZP + TFMPP and dexamphetamine. Surprisingly, the lateralised hemispheric function was not affected by TFMPP, and the directional asymmetry remained in those given TFMPP. It has been suggested that the hemispheres of the human brain are functionally specialised for certain cognitive processes, e.g. the right hand system may be superior in processing the sensory feedback compared to the left hemispheres which is primarily responsible for specifying the force parameters of the movement (Velay and Benoit-Dubrocard 1999), and the asymmetry patterns observed in cognitive tasks are related to the lateralisation of the associated cognitive functions, enabling efficient information transfer and processing (Lo et al. 2011). Neurochemical asymmetries are associated with the specialised functional roles of each hemisphere (Glick and Hinds 1985; Toga and Thompson 2003). It has been suggested that the left hemisphere is organised around a DA activation system, while the right hemisphere is organised around a NA arousal system (Fitzgerald 2012; Tucker and Williamson 1984; Xu et al. 2008). Neurochemical lateralisation in dopaminergic systems has been demonstrated in previous studies of rats (for example Glick and Hinds 1985; Rosen et al. 1984; Thiel and Schwarting 2001). Research on patients with schizophrenia have also supported DA lateralisation hypothesis and shown a normalisation of the high left-hemisphere activation after administration of neuroleptics, which are DA antagonists (Serafetinides 1973; Tomer and Flor-Henry 1989). Our findings of a lack of IHTT asymmetry in the groups given either BZP, BZP + TFMPP or dexamphetamine may suggest that enhanced DA release induced by these drugs promotes neural connectivity between the hemispheres which cancels out the asymmetry usually observed in healthy adults. Evidence shows that BZP and the combination of BZP + TFMPP selectively elevate dialysate DA levels in vivo (Baumann et al. 2004), and dexamphetamine increases dialysate DA concentrations up to 15 times above baseline in vivo (Miele et al. 2000). Conversely, TFMPP reduces extracellular DA via 5-HT_{2c} receptor binding, leading to the enhanced directional asymmetry.

It should be acknowledged that brain functional asymmetry involves more than a single neurotransmitter and that drug-induced effects on IHTT may be of a much more complex nature. Glutamate and γ-aminobutyric acid (GABA) are also thought to play a major role in the functional regulation of the corpus callosum (Bloom and Hynd 2005), which represents the major callosal fibre tracts connecting the two hemispheres (Cherbuin and Brinkman 2006; Westerhausen et al. 2004). Two contrasting roles have been suggested for the corpus callosum in brain asymmetry. According to the excitatory model, the corpus callosum serves an excitatory function, integrating information between hemispheres and facilitating the bilateral processing in order to maintain both hemispheres in a functionally activated state (Gazzaniga 2000). Hence, with increased callosal connectivity, the degree of lateralisation is reduced. In contrast, the inhibitory model proposes that the corpus callosum plays an inhibitory role, allowing for independent functioning of the hemispheres (Cook 1984; Gazzaniga 2000). Although concluding evidence for an excitatory or inhibitory callosal function is lacking, it has been argued that the function of the corpus callosum allows for a dynamic and flexible interaction between hemispheres rather than simply providing an automatic channel for exchange of information (Westerhausen and Hugdahl 2008). Functional inhibition or excitation of an individual

callosal connection can occur depending on the neurotransmitter, receptors and interneurons involved (Bloom and Hynd 2005). Amphetamine has been shown to dramatically increase extracellular concentrations of glutamate (Del Arco et al. 1999), while TFMPP has been shown to activate $GABA_B$ receptors via 5-$HT2_A$ receptors and also directly cause hypoglutamatergia by decreasing the extracellular glutamate levels (Golembiowska and Zylewska 1999; Srkalovic et al. 1994). It is possible that either BZP, BZP + TFMPP or dexamphetamine increases activation of the excitatory pathway in the corpus callosum which leads to a reduced degree of lateralisation, while TFMPP triggers the inhibitory function of the corpus callosum contributing to a greater degree of lateralisation.

Interpretations suggested by our findings need to be read with caution given the indirect nature of the evidence for either explanation. Additional research will be needed to clarify the anatomical and functional explanations for the observed different effects on IHTT induced by psychoactive compounds. Furthermore, given the nature of a randomised controlled trial, it is possible that there are significant group differences at baseline. However, according to the CONSORT (Consolidated Standards of Reporting Trials) statement, significance testing of baseline differences in randomised controlled trails should not performed (Moher et al. 2010). It has also been suggested that testing for baseline differences and choosing the group baseline difference in analyses can be misleading (de Boer et al. 2015).

Taken together, IHTT reflects the efficiency with which simple information is processed and transferred from one hemisphere to the other, and our findings highlight how the administration of BZP, TFMPP and BZP + TFMPP leads to changes in the pattern of information transfer. Alterations to the integrity of interhemispheric transfer under the influence of psychoactive compounds may provide an insight to the involvement of different neurotransmitters.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest in this research. The Health Research Council of New Zealand and the New Zealand Pharmacy Education Research Foundation funded this research but had no influence on any part of research process or preparation of this manuscript.

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