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ORIGINAL INVESTIGATION

Acute effects of the designer drugs benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) using functional magnetic resonance imaging (fMRI) and the Stroop task—a pilot study

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Abstract
Rationale A novel group of designer drugs containing benzylpiperazine (BZP) and/or trifluoromethylphenylpiperazine (TFMPP) have been available worldwide for more than a decade; however, their effects on human brain function have not been extensively described.
Objectives In a double-blind, placebo-controlled crossover study, the acute effects of BZP and TFMPP (alone and in combination) on the neural networks involved in executive function were investigated using an event-related Stroop functional magnetic resonance imaging (fMRI) paradigm.
Methods Thirteen healthy participants aged 18–40 years undertook the Stroop task 90 min after taking an oral dose of either BZP (200 mg), TFMPP (either 50 or 60 mg), BZP+TFMPP (100+30 mg) or placebo. A change in activity in neural regions reflects an increase in local demand for oxygen, due to an increase in neuronal activity.
Results Relative to placebo, an increase in neural activation was observed in the dorsal striatum following BZP, and in the thalamus following TFMPP, when performing the Stroop task.
Conclusion These data suggest that additional compensatory resources were recruited to maintain performance during the Stroop task. When BZP and TFMPP were administered together, both the dorsal striatum and thalamus were activated. However, the combination of BZP/TFMPP attenuated activation in the caudate, possibly due to TFMPP's indirect effects on dopamine release via $5HT_{2C}$ receptors.

Keywords Attention · Imaging · Functional MRI · Drug

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Introduction

A novel group of designer drugs containing benzylpiperazine (BZP) and/or trifluoromethylphenylpiperazine (TFMPP) have been marketed worldwide as safe and legal alternatives to illicit recreational drugs, such as 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine (MA), since the late 1990s. These drugs are used to enhance confidence, extend hours of socialising, induce euphoria and increase energy (Wilkins et al. 2006). The majority of BZP and/or TFMPP users are typically in their late teens and early twenties; however, these drugs are now illegal in the majority of countries.

Despite the extensive use of BZP, its effects on the human brain have not been thoroughly investigated. Studies examining the pharmacological effects of BZP in rats and monkeys show that it affects mainly dopamine (DA) release and reuptake, with additional but comparably smaller effects on both serotonin (5-HT) and noradrenaline (NA) release, similar to amphetamine (Baumann et al. 2005; Fekete et al. 1980). BZP is also thought to inhibit dopaminergic reuptake (Tekes et al. 1987) and act as an

agonist on postsynaptic dopaminergic receptors (Oberlander et al. 1979). Intravenously administered BZP (3 and 10 mg/kg) produced a dose-dependent elevation in extracellular DA and 5-HT concentrations in the nucleus accumbens (NAcc) of rats, although 5-HT release was only induced following high doses (Baumann et al. 2005). BZP has also been shown to cause the peripheral release of NA in the isolated rabbit pulmonary artery (Magyar 1987).

Behavioural studies using rodents have also reported that BZP has stimulant-like effects comparable to amphetamine and cocaine (Jones et al. 1980; Oberlander et al. 1979). The reported subjective and physiological effects of BZP in humans are similar to those produced by other psychostimulants such as MDMA and dexamphetamine (DEX) (Lin et al. 2009).

TFMPP is also a major component of many of these designer drug combinations, but rarely used alone and often combined with BZP. Historically, TFMPP has been extensively used as a biomarker for 5-HT activity (Miranda et al. 2002). Specifically, it affects 5-HT_{1B} and 5-HT_{2C} receptors that are thought to mediate its stimulus properties (Herndon et al. 1992). TFMPP, like MDMA, also stimulates 5-HT transporter-mediated release from neurons in vitro and in vivo (Auerbach et al. 1990; Baumann et al. 2005; Pettibone and Williams 1984). TFMPP also has an indirect effect on DA release via interactions with 5-HT_{2C} receptors and gamma-aminobutyric acid (GABA) blockade (Cloez-Tayarani et al. 1992; Millan et al. 1998; Nissbrandt et al. 1992), in addition to indirect effects on NA release via either 5-HT_{2C} or 5-HT_{1B} receptors (Millan et al. 1998; Sawynok and Reid 1992). Results from animal studies have shown some abuse potential because rats trained to discriminate MDMA from saline generalise to a TFMPP cue (Fantegrossi et al. 2005). However, TFMPP was not self-administered by rhesus monkeys trained to self-administer cocaine or amphetamine (Fantegrossi et al. 2005).

Importantly, when TFMPP (60 mg, oral) was given to human participants, its subjective effects were similar to fenfluramine and meta-chlorophenylpiperazine (mCPP) (Jan et al. 2010).

The ratio of BZP and TFMPP in these preparations ranges from 2:1 to 10:1 (Lin et al. 2011b). Baumann and colleagues (Baumann et al. 2005) reported that when BZP+TFMPP was given as a combination (1:1) to rats, parallel increases in dialysate 5-HT and DA release were observed. Low doses of BZP/TFMPP (3 mg/kg, i.v.) mimicked the effects of low-dose MDMA. However, Fantegrossi and colleagues (Fantegrossi et al. 2005) found that the combination of BZP/TFMPP (1:1) was a less effective reinforcer than BZP alone in adult rhesus monkeys. The authors consequently hypothesised that could be due to the agonist effects of TFMPP at 5HT_{2C} receptors that are known to reduce firing within the dopaminergic mesolimbic system (Di Matteo et al. 2001; Di Matteo et al. 2000).

Recent investigations into the subjective and physiological effects of these drugs reflect these reports, with data indicating that the combination shows similarities to DEX and MDMA (Lin et al. 2011b).

Comparing the effects of BZP and BZP+TFMPP with MA and MDMA raises concerns over their safety, because the chronic use of MDMA (McCann et al. 1998) and MA (Thompson et al. 2004) has been associated with mood disorders, long term deficits in memory and cognitive function and neurological abnormalities. Albeit the neurotoxicity of MDMA in people and the functional significance of its effects are a very controversial topic within the literature (Benningfield and Cowan 2013; Carvalho et al. 2012; Parrott 2012; Schouw et al. 2012). Research using the Stroop task, a task used to test selective attention and inhibition, reported that following chronic MA and cocaine use, there is a reduction in performance (Aron and Paulus 2007), which reflects the hypothesis that stimulant use alters an individual's ability to selectively attend to stimuli or inhibit prepotent responses.

Despite reported similarities between BZP, TFMPP and psychostimulants such as amphetamine, there is to our knowledge no published data describing the acute effects of BZP and TFMPP, as individual constituents or combined, on executive function of the human brain using functional magnetic resonance imaging (fMRI). The aim of this study was to investigate the effects of BZP and TFMPP, both alone and in combination, on the neural networks associated with attentional control and executive function using an event-related Stroop paradigm during fMRI. In this study, Stroop interference contrasts were used as a reflection of inhibitory performance whilst conducting the task.

The ratio and dose of BZP and/or TFMPP within the preparations available on the market varied to a large degree, however, previous studies by our laboratory have reported significant subjective effects to be obtained (with minimal side effects) at doses employed in this study (Jan et al. 2010; Lin et al. 2011a; Lin et al. 2011b). Whilst BZP was reported to have effects similar to those of other psychostimulants such as MDMA and DEX in humans, TFMPP was found to be similar to other serotonergic drugs such as mCPP.

Materials and methods

Thirteen non-smoking healthy participants (seven female and six male; aged 18–40 years) were recruited to participate in a double-blind, placebo-controlled crossover trial. Approval for this study was granted by the Northern X Regional Ethics Committee of NZ (Ethics approval number NTX/07/08/078). Participants attended an initial screening session where written consent was obtained. Participants were excluded if they had a history of mental illness, cardiac disease, head trauma, endocrine disorders, epilepsy, were pregnant or breastfeeding. Three data sets were rendered unusable due to faults in E-prime files (one from each group), which left 12 subjects in each group.

A custom designed questionnaire was completed by each participant detailing their medication history, recreational

drug, alcohol and cigarette use, sleeping patterns and stress levels to ensure they were not drug naive or current or past heavy recreational drug users. Regular drug users for the purpose of our study were classified as those who had used illicit substances more than four times per month for several months. To ensure a complete history of drug use, participants were also asked about their use of all medications, including prescription medications that they have obtained and used without a prescription.

Drugs

Benzylpiperazine hydrochloride (200 mg), trifluoromethylphenylpiperazine (50 mg for participants weighing <60 kg or 60 mg if >60 kg) benzylpiperazine and trifluoromethylphenylpiperazine (100+30 mg, respectively) and placebo (methylcellulose) were given to participants in a randomised order. All capsules were identical in appearance and were manufactured using good manufacturing practise by the School of Pharmacy, University of Auckland, NZ.

Procedure

The Stroop paradigm is used to investigate the cognitive domains of selective attention and inhibition. Participants are required to respond to one of three conditions, that is, neutral (control) words comprised of a non-colour word, congruent words where a colour word is presented in its matching colour and incongruent words where the colour of the word and the colour of its presentation do not match. When the incongruent condition is presented there is a prepotent response to respond to the written word rather than its colour. An inability to suppress this prepotent response and respond to the weaker but task-relevant response is said to reflect impulsivity and impaired selective attention. This is known as the Stroop interference effect.

Participants fasted for 12 h before the trial and were asked to abstain from alcohol or caffeine from the evening prior to testing. Participants were excluded from the trial if they were found to be positive by urinalysis test kit for recreational drug use or pregnancy on the day of testing.

Prior to drug administration participants completed a practise version of the colour-word Stroop task to ensure a minimum accuracy of 75 %. Drug or placebo capsules were given with 250 mL of water 90 min before imaging. The time taken to reach peak plasma concentrations of BZP is 75 min (Antia et al. 2009) and TFMPP is 90 min (Antia et al. 2010). During this time, participants remained in the presence of researchers in a comfortable area with minimal stimulation. Participants were then tested during fMRI after taking each drug or placebo using a randomised double-blind schedule with a minimum of 7 days between sessions.

fMRI data analysis and acquisition

fMRI was performed at the Centre for Advanced MRI at The University of Auckland. The Stroop paradigm was presented on a screen located 3.5 m from the participants and visible via a prism built into the head restraint used to minimise head movements during imaging. Control, congruent, incongruent and rest (fixation cross) conditions were presented to the participants. Each trial consisted of 180 presentations: 36 congruent, 36 incongruent, 72 control and 36 rest fixation crosses. Each stimulus was presented for 2000 msec and was presented with a pre-determined randomisation, this ensured that no negative priming occurred and that each time the participant undertook the task, a different order of randomisation was presented. Participants were instructed to respond to the colour of the presented word as soon as it appeared on the screen using two, two-buttoned, hand-held response boxes (one in each hand) to minimise potential head movement caused by vocalisation. Each button was assigned a colour (from left to right—red, green, blue and yellow).

Blood oxygen level dependent (BOLD) functional images were acquired using a T2*-weighted echo planar imaging (EPI) sequence with a 1.5 T Siemens Magnetom Avanto scanner: TR 3000 ms, TE 50 ms, FOV 192 mm, in-plane voxel size 3.0 mm×3.0 mm, flip angle 90°, 29 slices, slice thickness 4.0 mm no gap. On each trial day, 157 volumes were collected for each participant per run and two runs were completed during each visit with a 30-s break between runs. For anatomical reference, a high-resolution structural MPRAGE image was acquired at the end of the first session on each trial day.

Raw data were analysed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB version 7.8.0 (Mathworks, Sherborn, MA, USA). After co-registration to the T1-weighted structural volume, EPI images were normalised to standard space (Montreal Neurological Institute [MNI] template) at a voxel size of 2×2×2 mm. Images were spatially smoothed using an isotropic Gaussian kernel of 8 mm full-width at half-maximum (FWHM) in the x, y and z axes. Incorrect and non-responses to the Stroop paradigm were not eliminated from analysis because the accuracy was greater than 90 % in all cases.

Outliers due to movement or signal from pre-processed EPI files using thresholds of 3 SD from the mean, 0.75 mm for translation and 0.02 rad rotation were removed from the data sets using ART repair (Mazaika et al. 2009). An F test across all conditions was carried out per session to ensure each subject displayed activity in the visual cortex following first level analysis.

First level analysis allowed for an individual's activation to be evaluated for the three conditions, that is, congruent, control and incongruent. For this colour-word Stroop paradigm, we generated three T contrasts across the runs for each subject to allow group analysis at the second level: (a) congruent, (b)

incongruent and (c) control conditions. No interaction contrasts were made at this stage to maintain maximum specificity for second level analysis.

T contrasts were subsequently used in the second level group comparison. Event-related responses to the Stroop effect (incongruent minus congruent) were defined and the analysis divided into three parts for each drug state: (1) BZP, (2) TFMPP and (3) BZP+TFMPP. For these drug states, inter-drug state comparisons were individually compared to placebo by constructing F interaction contrasts. Main effect of task and main effect of drug were also derived for each drug comparison i.e. (1) BZP and placebo data, (2) TFMPP and placebo data, (3) BZP+TFMPP and placebo data and (4) BZP and TFMPP data.

Voxel-wise analysis was conducted using fMRI data initially with a FWE correction of 0.05. For data that did not yield FWE-corrected results, significant voxels were required to pass a voxel-wise statistical threshold determined by 3DClustSim. The program was provided with the number of voxels in the group map, the spatial correlation of voxels and the voxel-wise threshold. The program then runs a series of Monte Carlo simulations (10,000 iterations) to determine the frequency of clusters of varying sizes produced by chance. From this frequency distribution, we then select the cluster size (152 given our parameters) that occurs <1 % of the time by chance, to give a threshold of $p<0.01$ (corrected). For the interaction effect between drug and placebo, there were no clusters greater than this threshold. Thus a significance threshold of $p<0.005$ uncorrected was used and the results presented as an exploratory analysis.

Anatomical locations were derived using a customised script in SPM8 (McLaren and Ph.D. Postdoctoral Research Fellow 2011a). Parameter estimates were interpreted as the percentage BOLD change in relation to the whole brain mean (McLaren and Ph.D. Postdoctoral Research Fellow 2011b), referred to as percentage BOLD signal change, allowing the determination of the direction of activation. Significant clusters of activation were displayed using a single subject T1 template from SPM.

Behavioural data (accuracy [Ac] and reaction time [Rt]) were analysed using SPSS and a repeated measures ANOVA for both condition effect and group (drug state)×condition effect. Rt data were filtered to display correct responses only. The behavioural data was also compared using the Kruskal-Wallis test, a non-parametric analysis in SPSS, due to the distribution of Ac for all conditions being skewed to the right-hand side (i.e. they all performed to a high accuracy). All analyses were performed using the SPSS version 22.0 software and statistical significance was taken at $p<0.05$.

Results

Behaviourally, the expected Stroop effect was found within each drug condition. That is, the Rt in the incongruent condition (within groups) was significantly larger than that of the control condition ($p<0.05$). There was no significant main effect for drugs, nor was there a significant interaction (Table 1). There were no significant differences in intra-, or inter-group Ac (Table 2). The Kruskal-Wallis test also showed no significant differences between drug conditions.

The imaging analysis assessed main effect of task, main effect of drug and regional differences in neural network activations. Regional differences between drug conditions were assessed using an F-contrast to examine the Stroop interaction (incongruent minus congruent) (see Table 3).

Main effects

Main effect of both task and drug were tested for each set of data i.e. for each drug group and the corresponding comparative data (Table 3). For each main effect of task, there was

Table 1 Mean Rt (msec)±the SE for each Stroop condition after taking either BZP, TFMPP or BZP+TFMPP in comparison to placebo

Rt (msec)						
Drug state	BZP			Placebo		
Condition	Cong	Control	Incong	Cong	Control	Incong
Mean Rt (msec)	721.67	742.67	873.28	739.79	778.54	868.9
Standard error	35.39	36.15	36.09	35.39	36.15	36.09
Drug state	BZP+TFMPP			Placebo		
Condition	Cong	Control	Incong	Cong	Control	Incong
Mean Rt (msec)	737.7	775.69	909	711.82	757.5	856.42
Standard error	23.19	24.18	21.68	23.19	24.18	21.68
Drug state	TFMPP			Placebo		
Condition	Cong	Control	Incong	Cong	Control	Incong
Mean Rt (msec)	762.25	823.05	938.8	747.68	795.6	880.08
Standard error	38.07	40.54	37.34	38.07	40.54	37.34

Cong congruent, *incong* incongruent

Table 2 Mean Accuracy±the SE for each Stroop condition after taking either BZP, TFMPP or BZP+TFMPP in comparison to placebo

Accuracy of response to Stroop conditions						
Drug state	BZP			Placebo		
Condition	Cong	Control	Incong	Cong	Control	Incong
Mean Ac	0.98	0.99	0.97	0.97	0.98	0.97
Standard error	0.01	0.01	0.01	0.01	0.01	0.01
Drug state	BZP+TFMPP			Placebo		
Condition	Cong	Control	Incong	Cong	Control	Incong
Mean Ac	0.98	0.98	0.97	0.97	0.98	0.96
Standard error	0.01	0.01	0.01	0.01	0.01	0.01
Drug state	TFMPP			Placebo		
Condition	Cong	Control	Incong	Cong	Control	Incong
Mean Ac	0.97	0.98	0.98	0.97	0.98	0.96
Standard error	0.01	0.01	0.01	0.01	0.01	0.01

Cong congruent, *incong* incongruent

FWE-corrected results attained ($p<0.05$). Group 1 (participants who had been administered BZP and the corresponding placebo data) main effect of task resulted in significant areas of activation in the anterior cingulate cortex (ACC), inferior frontal, mid-frontal and inferior parietal gyri, insula and precuneus. Group 2 (participants who had been administered TFMPP and the corresponding placebo data) main effect of task resulted in activation in the insula. Group 3 (participants who had been administered the combination of BZP+TFMPP and the corresponding placebo data) main effects of task resulted in activation of inferior parietal region. Group 4 (participants who had been administered BZP and the corresponding TFMPP data) main effect of task resulted in activation of inferior frontal gyrus and bilateral insula.

Main effects of drug condition were also tested, there was no corrected supra-threshold clusters of activation for any of the drug comparison groups.

Table 3 Neural correlates of activation of 'main effect of task'

Anatomical region	MNI coordinates			*F* value	Cluster size
	x	*y*	*z*		
Group 1 (Data from the BZP condition comparison to placebo)					
'Cingulum_Ant_L'	−8	36	−6	52.36	11
'Frontal_Inf_Oper_L'	−42	6	28	44.51	17
'Insula_R'	32	28	0	41.26	2
'Frontal_Mid_L'	−26	26	42	40.89	2
'Parietal_Inf_L'	−48	−40	44	39.83	2
'Frontal_Mid_Orb_L'	−8	48	−6	39.17	1
'Precuneus_R'	10	−52	24	38.12	1
Group 2 (Data from the TFMPP condition comparison to placebo)					
'Frontal_Inf_Oper_L'	−44	4	26	52.62	31
Group 3 (Data from the BZP+TFMPP condition comparison to placebo)					
'Parietal_Inf_L'	−45	−36	44	46.55	14
Group 4 (Data from the BZP comparison with TFMPP)					
'Frontal_Inf_Tri_R'	46	30	20	47.59	6
'Insula_R'	32	24	2	46.41	3
'Insula_L'	−28	20	6	41.19	1

The *F* value at the peak voxel within each cluster is reported

FWE-corrected $p<0.05$

Drug condition×stroop interaction

The BZP drug state compared to placebo, yielded activations at the significance level of $p<0.005$ uncorrected (extent threshold of 5 voxels). Parameter estimates were derived for the congruent and incongruent conditions at each significant coordinate to determine the direction of the activation change.

In comparison to placebo, BZP induced four significant clusters in the bilateral caudate (Fig. 1), left inferior temporal gyrus and right superior occipital gyrus (Table 4, Section A). The cluster in the caudate was found to be due to increased activation during the incongruent condition, the left inferior temporal gyrus showed decreased activation during the incongruent condition and the right superior occipital gyrus cluster is derived from the attenuation of the BZP incongruent condition to a lesser extent than following placebo.

TFMPP, in comparison to placebo, induced four clusters: three in the right thalamus (Fig. 2) and one in the left lingual gyrus (Table 4, Section B). The percentage BOLD signal change indicated that all three clusters displayed greater activation following TFMPP in the incongruent condition and that lingual activation increased in the TFMPP congruent condition compared to placebo.

When BZP and TFMPP were given together and compared to placebo, activation occurred in the thalamus, right caudate and left inferior temporal gyrus (Table 4, Section C). Percentage BOLD signal change plots identified that the cluster in the thalamus was due to increased activation following BZP+TFMPP in the incongruent

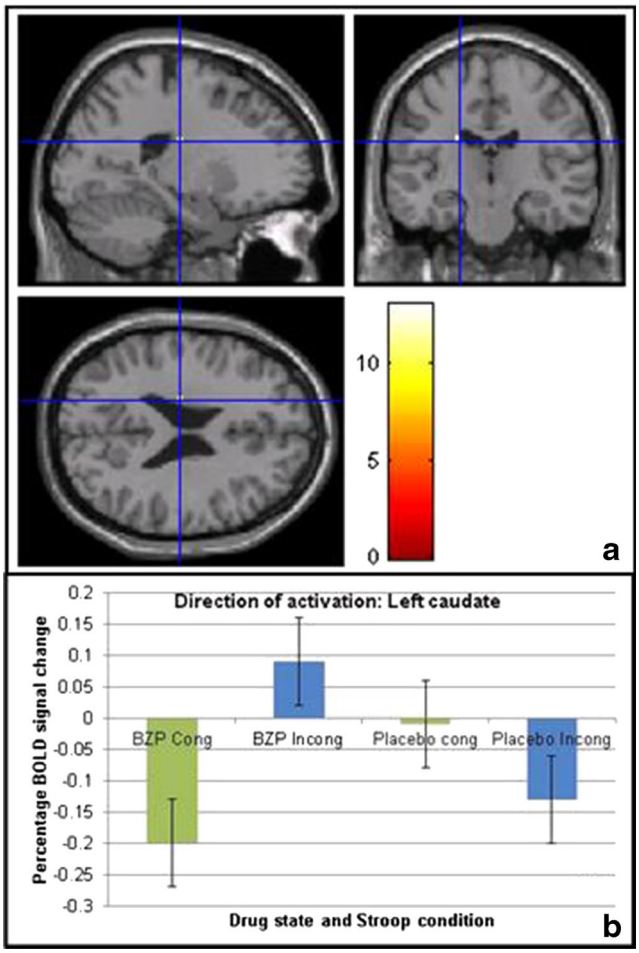

Fig. 1 Activations associated with the Stroop interference contrast: when BZP is contrasted to placebo $p<0.005$ uncorrected; cluster threshold >5 voxels. **a** Activation in the left caudate and **b** plot of parameter estimates, indicating the direction of activation in the left caudate

condition (similar to that caused by TFMPP alone). However, the caudate showed *reduced activation* following the combination of BZP and TFMPP in the congruent condition in comparison to placebo.

To highlight the unique effects of BZP and TFMPP in response to the Stroop task, we compared and contrasted the responses for the Stroop effect following their individual administration to each other i.e. BZP was compared to TFMPP (Table 4, Section D). Differences occurred in the left anterior cingulate cortex, pre and post central gyri, superior and mid frontal gyri, parietal gyrus, right calcarine and right cerebellum, left para hippocampal gyrus and rolandic operculum. In comparison to BZP, TFMP P caused less deactivation of the ACC, orbital mid frontal and superior frontal gyri. In comparison to BZP, the mid central gyrus, precentral, postcentral and parietal gyri were deactivated during the incongruent TFMPP condition. BZP induced greater activation of the cerebellum and rolandic operculum, and deactivation in the para hippocampal gyrus .

Discussion

This study was a pilot study to investigate the acute effects of BZP and TFMPP both alone and in combination in comparison to placebo on the neural networks associated with selective attention and inhibition using an event-related Stroop paradigm during fMRI. Stroop interference contrasts were used to reflect inhibitory performance whilst conducting the task. It is generally agreed that the behavioural effects induced by the Stroop paradigm are due to a conflict between a prepotent response and a weaker task-relevant response (Heflin et al. 2011; Stroop 1935).

With respect to behavioural performance, the expected trends in reaction time reflective of the Stroop effect were found within drug groups. However, Ac and Rt were not significantly affected by each drug or the combination. In contrast, although no large effect sizes were detected, the fMRI analysis showed some distinct drug-induced differences. These changes in activation are a reflection of a change in processing to some degree, and, as discussed below, likely reflect changes in the resources allocated to task performance. Regional activation during the Stroop paradigm has been reported predominantly in the anterior cingulate cortex (ACC) (Posner and Dehaene 1994) and dorsolateral prefrontal cortex (DLPFC) (Badzakova-Trajkov et al. 2009), although their respective roles have been disputed. As our study focused on drug-induced effects during the Stroop paradigm, we hypothesised that we could identify activation in additional areas that would reflect drug-induced changes in neural processing.

When considering the main effect of task, group 1 (BZP drug condition and corresponding placebo data) induced significant corrected results in the ACC and the inferior frontal gyrus, all of which have been associated with response inhibition associated with the Stroop task, and insula activation that has been found to be activated in response to the incongruent condition of the Stroop task (Salo et al. 2009). When BZP was contrasted to placebo for the Stroop effect, the interaction induced regional activation in the bilateral caudate, left inferior temporal gyrus and right superior occipital gyrus when compared to placebo. We believe activation of the temporal and occipital gyri were likely due to processing visual stimuli. Dopaminergic modulation is reportedly involved in the guidance of attention towards relevant locations and in the cognitive processing of visual stimuli (Mogami and Tanaka 2006; Vitay and Hamker 2007).

The effects of BZP are mainly dopaminergic, with lesser effects on noradrenergic and serotonergic pathways. The mesocorticolimbic DA system, which includes the dorsal striatum (caudate and putamen) is implicated in reward processing. The caudate, rich in DA receptors, is reported in part to mediate the relationship between action and reward outcome (da Silva Alves et al. 2011) and is

Table 4 Neural correlates of activation of drug state in comparison to placebo for the Stroop interaction:incongruent (incong)-congruent (cong)

Anatomical region	MNI coordinates			*F* value	Cluster size	Directionality: contrast estimates and standard error (SE)				
	x	*y*	*z*			Drug cong	Drug incong	Placebo cong	Placebo incong	SE
A. BZP×placebo interaction $p<0.005$ uncorrected										
'Occipital_Sup_R'	26.00	−78.00	44.00	13.06	14	−0.46	−0.01	−0.63	−0.94	0.13
'Caudate_L'	−20.00	−18.00	24.00	12.09	9	−0.20	0.09	−0.01	−0.13	0.07
'Temporal_Inf_L'	−52.00	−24.00	−18.00	11.25	9	0.04	−0.26	0.12	0.27	0.08
'Caudate_R'	18.00	14.00	2.70	10.77	13	0.04	0.36	0.39	0.21	0.09
B. TFMPP×placebo interaction $p<0.005$ uncorrected										
'Thalamus_R'	16.00	−24.00	8.00	25.68	69	−0.18	0.09	0.12	−0.14	0.07
'Thalamus_R'	18.00	−26.00	0.00	11.06	69	0.05	0.21	0.16	−0.01	0.07
'Thalamus_R'	8.00	−12.00	2.00	21.03	44	−0.10	0.30	0.20	−0.06	0.10
'Lingual_L'	−24.00	−72.00	−4.00	18.25	48	0.23	−0.22	−0.03	0.14	0.10
C. BZP/TFMPP×placebo interaction $p<0.005$ uncorrected										
'Thalamus_R'	17.00	−14.00	11.00	13.82	25	−0.06	0.29	0.16	−0.02	0.09
'Thalamus_L'	−8.00	−10.00	0.00	12.70	11	0.02	0.39	0.10	0.07	0.07
'Caudate_L'	−7.00	7.00	12.00	12.26	9	−0.45	−0.20	−0.14	−0.36	0.08
'Temporal_Inf_L'	−46.00	−16.00	−24.00	10.07	5	0.08	−0.27	−0.17	0.00	0.10
D. BZP×TFMPP interaction $p<0.005$ uncorrected										
'Cingulum_Ant_L'	−2.00	36.00	−6.00	23.99	121	−0.24	−1.01	−0.48	−0.47	0.10
'Frontal_Mid_Orb_R'	14.00	42.00	−4.00	9.95	121	−0.06	−0.53	−0.10	−0.02	0.11
'ParaHippocampal_L'	−28.00	−32.00	−16.00	19.88	25	−0.01	−0.47	−0.24	−0.11	0.08
'Postcentral_L'	−40.00	−18.00	40.00	18.64	57	0.00	0.12	0.20	−0.32	0.09
'Calcarine_R'	18.00	−66.00	18.00	15.73	20	−0.76	−0.37	−0.28	−0.43	0.08
'Frontal_Sup_R'	18.00	62.00	4.00	15.54	12	−0.13	−0.41	−0.68	−0.08	0.14
'Cerebelum_4_5_R'	10.00	−48.00	−12.00	15.09	10	0.41	0.75	0.27	0.05	0.09
'Rolandic_Oper_L'	−46.00	−16.00	18.00	14.30	5	0.05	0.29	0.46	0.12	0.10
'Frontal_Mid_L'	−32.00	56.00	22.00	12.32	15	−0.42	-0.03	0.35	−0.21	0.17
'Postcentral_R'	64.00	−14.00	38.00	11.41	6	0.50	0.70	0.69	0.09	0.15
'Precentral_R'	20.00	−26.00	68.00	11.33	15	−0.20	0.00	−0.03	−0.42	0.11
'Parietal_Sup_R'	17.00	−46.00	65.00	11.12	17	−0.22	0.00	−0.20	−0.54	0.11
'Postcentral_R'	22.00	−40.00	68.00	9.54	17	−0.11	0.03	0.01	−0.49	0.13

The *F* value at the peak voxel within each cluster is reported. Note: All clusters are significant at $p<0.005$ (uncorrected), cluster threshold of 5 voxels. *Cong* congruent, *incong* incongruent, *SE* standard error

also said to contribute to the ability to learn through reinforcement (Delgado et al. 2005). Since BZP affects dopaminergic neurons, we initially considered that the overall increase in DA release increased activation within the caudate, rather than the task itself. However, if this was the only factor, the change we observed in the bilateral caudate would also show increased activation during the congruent and incongruent conditions, which did not occur, which leads us to assume that it is partially a task-related change in processing causing activation.

Zink and colleagues (Zink et al. 2004) suggest that caudate activity is closely linked to the behavioural relevance of the stimuli. In our study, the bilateral caudate was activated following BZP during the incongruent condition. Therefore, this could be an aid to learning, which requires suppression of the prepotent response and responding to the weaker task-relevant stimuli.

The activation in the caudate may be a result compensatory recruitment after the administration of BZP. It has been suggested that the head of the caudate controls interference. An fMRI study of healthy participants completing the Stroop and Simon tasks with the aim of investigating both word and spatial interference, respectively, found the head of the left caudate was activated during Stroop interference only (Green et al. 2010). This suggests the caudate plays a role in the control of word but not spatial interference (Peterson et al. 2002). In addition, Li et al. (Li et al. 2008) demonstrated that during a stop-

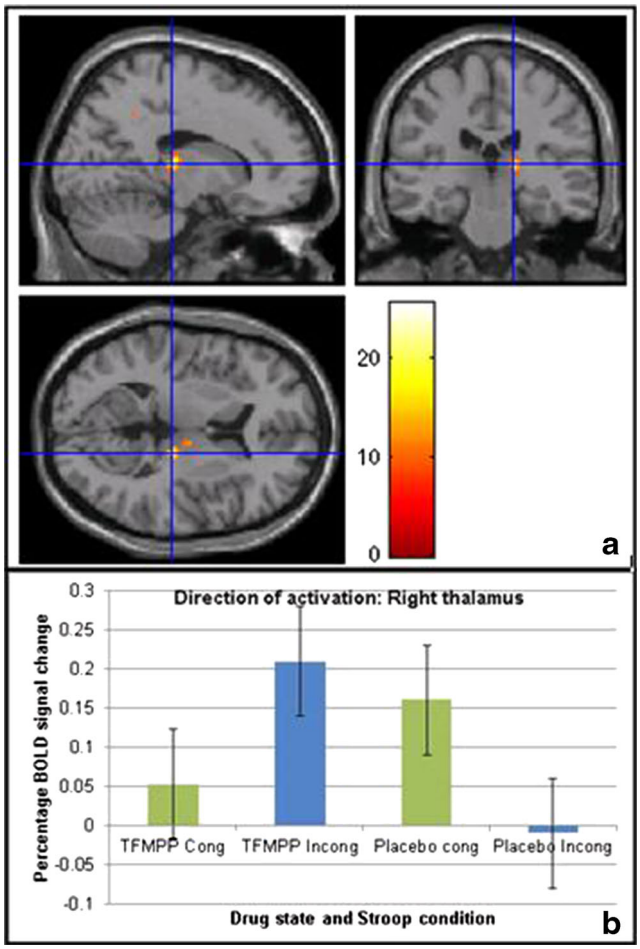

Fig. 2 Activations associated with the Stroop interference contrast: when TFMPP is contrasted to placebo $p<0.005$ uncorrected; cluster threshold >5 voxels. **a** Activation in the right thalamus and **b** plot of parameter estimates, indicating the direction of activation in the right thalamus

signal reaction task the caudate plays a role in the inhibitory control of prepotent responses.

We propose BZP impairs the ability to attend to task-relevant information during the task, thus requiring recruitment of the caudate as a compensatory mechanism, either as an aid to learning or for inhibitory control, which allowed participants to perform to the same standard as they had following placebo, and is needed in addition to the resources usually needed to perform the Stroop task, for example the ACC and insula, which was found in the main effect of task. This may be due to the inverted U-shaped dose-response curve that has been proposed to describe the effect of DA transmission on executive function. It has been suggested that there is an optimum extracellular DA level (Arnsten 1998), and DA transmission that is too high or too low within the dopaminergic circuitry results in sub-optimal performance on tasks (Arnsten 1998).

Whilst we interpret the increased activity of caudate as a compensatory response, it is important to note that there were no differences in reaction time speed or accuracy following either BZP or placebo which also supports this hypothesis. It is possible that caudate activity may be due to an increase in the function of the area because BZP is dopaminergic and could act as a cognitive enhancer. However, the behavioural data does not support this so a direct comparison with amphetamine seems warranted.

The main effect of task, group 2 (TFMPP drug condition and corresponding placebo data) induced significant corrected results in insula activation, as mentioned, the insula is a region that has been found to be activated in response to the incongruent condition in the Stroop task (Salo et al. 2009). TFMPP, in contrast to BZP, is a 5-HT agonist, and when contrasted to placebo, TFMPP induced four clusters of activation: three in the right thalamus and one in the left lingual gyrus. The lingual gyrus is activated following the presentation of visual stimuli. In research by Andrews and Anderson (Andrews and Anderson 1998) fenfluramine, also a serotonergic agonist, increased flicker fusion threshold suggesting 5-HT enhances early stage visual information processing, and thus accounting for changes in activation following TFMPP administration.

Associations between 5-HT, inhibition and attention have been reported. For example, rodent studies demonstrated a modulatory role for 5-HT in inhibitory control processing (Winstanley et al. 2004a). However, it has been proposed that different 5-HT receptor subtypes have opposing effects, that is, activation of 5-HT_{2A} receptors enhances DA release (Winstanley et al. 2004b), and in contrast, 5-HT_{2C} activation inhibits DA release (Di Matteo et al. 2001; Di Matteo et al. 2000; Millan et al. 1998). After administration of SB 242084 (a 5-HT_{2C} receptor antagonist) rodents completing the five-choice serial reaction time task showed an increase in premature responding and a decreased latency indicating that 5-HT_{2C} receptors play a role in regulating behavioural inhibition (Winstanley et al. 2004b). TFMPP's stimulus effects are thought to be mediated by $5HT_{2C}$ receptors, and thus might reduce DA release.

An fMRI study investigating the effects of mCPP on humans reported an enhanced response within the lateral orbitofrontal cortex (OFC) and no significant change in behavioural effects (Anderson et al. 2002). mCPP, like TFMPP, is a $5HT_{2C}$ agonist and also found in some designer drug combinations. The areas of activation observed following administration of mCPP were consistent with the hypothesis that 5-HT affects inhibitory responses. Therefore, we hypothesised that TFMPP would also impair behavioural performance during the Stroop task; however, we did not find this.

The thalamus, rich in 5-HT reuptake sites, is affected by antidepressants. Serotonergic pathways play an important role in modulating behavioural arousal (Waterhouse et al. 1986). After administering TFMPP, we observed an increase in thalamic activation, so we propose that this region was recruited in a compensatory manner allowing participants to maintain attention on the task in the presence of altered arousal.

Attention and arousal are two cognitive domains that are linked. Whilst attention is governed mainly by cortical systems, arousal is governed mainly by subcortical structures, however, both domains share an important anatomical structure i.e. the thalamus (Portas et al. 1998).

There have been similar reports of compensatory recruitment mediating attentional processes. For example, clonidine, an α_1/α_2 agonist, also reduced sustained attention and reduced activation in the thalamus. When participants were required to complete a task requiring attention during imaging, the thalamus showed increased activation (Coull et al. 1997). The effects of clonidine were thought to reflect its effects on cortical arousal, thus the thalamus was only recruited to complete the task.

Further to this hypothesis, the function of the thalamus has been described as a gateway for cortical signalling (Vollenweider and Geyer 2001). It is part of the cortico-striato-thalamo-cortical loop and plays a key role in controlling or 'gating' information to the cortex (Newman 1995) and consequently involved in regulating the level of awareness and attention attributed to specific stimuli. Studies have shown that the greatest amount of information transfer to the thalamus occurs whilst a person is awake (Coenen 1998), especially when attention is required for a task.

In subjects that have no disturbances in monoaminergic systems, DA and 5-HT have inhibitory influences on the striatum (Carlsson and Carlsson 1990). GABAergic input from the striatum and the pallidum is thought to have an inhibitory effect on the neurons in the thalamus. This inhibition should act in a protective manner, as the result should be a reduction in sensory input into the cortex from the thalamus. Therefore, if there is an increase in DA or 5-HT, this may lead to a reduction in the inhibitory influence of the striatum and open this thalamic filter, possibly leading to an overload of sensory information to the cortex (Vollenweider and Geyer 2001). Therefore, the thalamic activation that we observe following TFMPP may be a reflection of this gating influence being modulated by the disturbance in 5-HT and DA transmission.

As stated previously, TFMPP predominantly induces 5-HT release, with indirect effects on dopaminergic and adrenergic transmission in the frontal cortex (Millan et al. 1998). Therefore, the increased thalamic activation we observed could be a result of increased serotonergic activity leading to reduced dopaminergic activity and subsequently, reduced inhibition in the thalamus.

When BZP and TFMPP were given in combination, activation of both the thalamus and the left dorsal striatum occurred. The increased activation of the thalamus was similar to that induced by TFMPP alone, whilst caudal activation induced by BZP alone and in combination with TFMPP was not the same. Further analysis revealed that the activation arose from different conditions. Increased caudal activation induced by BZP occurred during the Stroop incongruent condition. In contrast, BZP combined with TFMPP induced activation resulted from attenuation during the congruent condition in comparison to placebo.

We hypothesised that changes in activation induced by BZP combined with TFMPP would reflect the changes we observed after giving them individually but this did not occur uniformly. The subsequent attenuated activation of the caudate suggests that when BZP and TFMPP are combined, it is likely that their differential effects on dopaminergic and serotonergic neurons are responsible. TFMPP is thought to have opposing effects on dopaminergic activity because it is a $5HT_{2C}$ receptor agonist and therefore inhibits firing within the dopaminergic mesolimbic system (Di Matteo et al. 2001; Di Matteo et al. 2000). Consequently, a comparative reduction in DA release compared to that observed following BZP alone may be responsible. Furthermore, this is reflected by research that found a combination of BZP and TFMPP was a less effective reinforcer than BZP alone in rhesus monkeys (Fantegrossi et al. 2005).

What is clear from our results is that each drug induces a unique pattern of activation. Overall, we believe these differences are due to each drug's individual effects on dopaminergic and serotonergic pathways.

The event-related Stroop paradigm we used was of moderate length, and the participants were asked to repeat the task every 7 days to complete the overall trial (i.e. after taking each drug/placebo), which could have led to a learned response to the Stroop effect. Therefore, the trial was designed to give each drug/placebo in a randomised order to ensure that any learned effect had limited impact.

We also chose doses of BZP and/or TFMPP based on our laboratory's past research, that is, doses known to evoke behavioural responses whilst avoiding drug-induced adverse effects. It is likely that higher doses than those used in this trial may result in differential effects. Past research in our laboratory has found subjective and physiological differences of BZP, TFMPP and BZP in combination with TFMPP to placebo (Jan et al. 2010; Lin et al. 2009; Lin et al. 2011a). Specifically that BZP induced significant dexamphetamine-like stimulant effects, inducing euphoria, sociability, and drug liking. TFMPP induced fewer stimulant-like effects and increased anxiety, thought to be due to its serotonergic effects. When BZP and TFMPP were administered together (at lower doses that that of individual administration) the effects on blood pressure and subjective effects were similar to that of other stimulants.

In addition, in a gambling task, we also found that there were differences in activation in response to anticipation of an uncertain event (Curley et al. 2013). BZP appeared to reduce response to uncertainty, shown via a decreased response in the inferior frontal gyrus, insula and occipital regions in comparison to placebo. TFMPP, on the other hand, increased the

activation of the putamen but decreased the activity in the insula relative to placebo.

The current data was an exploratory study to evaluate whether there were any differences in response to inhibition and selective attention after a single dose of the novel drugs BZP, TFMPP and the combination of BZP and TFMPP in comparison to placebo. Although our results were not corrected for multiple comparisons, we believe the results may reflect that there are differences in task-related behaviour after single doses of these novel drugs. In addition, we believe this is due to the small sample size. Whilst it is possible that the results may reflect a type-I error, we do not believe this is likely. The regions affected following drug administration in comparison to placebo are also involved in processing attention and/or inhibition. In addition, when the two drugs were given in combination at a lower dose than when they were given individually, the same regional activity was observed, which also suggests that these results are not due to a type-I error. A larger sample could be tested in future experiments to evaluate whether these results reach significance. Power analyses suggests using fMRI variables support a sample size of 18 participants per group is required to achieve a power of 80 % (Nichols 2008).

Conclusion

This study is the first to investigate the effects of the relatively new designer drugs BZP and TFMPP both alone and in combination on selective attention and impulsivity using fMRI. Whilst no significant behavioural effects during the Stroop task were observed, we found separable drug-induced changes in regional activation. BZP increased activation in the dorsal striatum possibly due to an inability to attend to task-relevant information. TFMPP induced thalamic activation, suggesting that compensatory resources were recruited that allowed participants to perform the Stroop task to the same standard as after administration of placebo. When the BZP and TFMPP were given together, there was activation in both the thalamus and the dorsal striatum, albeit caudal activation was attenuated by this combination.

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Conflict of interest The authors declare no conflict of interest.

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