Assessment of the Acute Effects of 2C-B vs. Psilocybin on Subjective Experience, Mood, and Cognition

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2,5-dimethoxy-4-bromophenethylamine (2C-B) is a hallucinogenic phenethylamine derived from mescaline. Observational and preclinical data have suggested it to be capable of producing both subjective and emotional effects on par with other classical psychedelics and entactogens. Whereas it is the most prevalently used novel serotonergic hallucinogen to date, it's acute effects and distinctions from classical progenitors have yet to be characterized in a controlled study. We assessed for the first time the immediate acute subjective, cognitive, and cardiovascular effects of 2C-B (20 mg) in comparison to psilocybin (15 mg) and placebo in a within-subjects, double-blind, placebo-controlled study of 22 healthy psychedelic-experienced participants. 2C-B elicited alterations of waking consciousness of a psychedelic nature, with dysphoria, subjective impairment, auditory alterations, and affective elements of ego dissolution largest under psilocybin. Participants demonstrated equivalent psychomotor slowing and spatial memory impairments under either compound compared with placebo, as indexed by the Digit Symbol Substitution Test, Tower of London, and Spatial Memory Task. Neither compound produced empathogenic effects on the Multifaceted Empathy Test. 2C-B induced transient pressor effects to a similar degree as psilocybin. The duration of self-reported effects of 2C-B was shorter than that of psilocybin, largely resolving within 6 hours. Present findings support the categorization of 2C-B as a psychedelic of moderate experiential depth at doses given. Tailored dose-effect studies are needed to discern the pharmacokinetic dependency of 2C-B's experiential overlaps.

Study Highlights

☑ **WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

☑ To date, 2,5-dimethoxy-4-bromophenethylamine (2C-B) is the most frequently used novel serotonergic psychedelic among recreational users. Despite this, no clinical data exist pertaining to its safety and general acute effects.

☑ **WHAT QUESTION DID THIS STUDY ADDRESS?**

☑ The acute subjective, cognitive, cardiovascular, and pharmacokinetic profile of 2C-B (20 mg) was investigated in healthy participants using placebo and psilocybin (15 mg) as comparators.

☑ **WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

☑ The present data further supports the categorization of 2C-B as a psychedelic with entactogenic properties. Well-matched and well-tolerated, 20 mg 2C-B produced less subjective impairment and emotional lability than 15 mg psilocybin. Cardiovascular stimulation and cognitive impairment were comparable between both drugs.

☑ **HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

☑ These results highlight for the first time a novel psychedelic phenethylamine for clinical study. Future dose-ascending and longitudinal studies will serve to define 2C-B's place in psychedelic-assisted psychotherapy.

Classical psychedelics are a diverse set of psychoactive compounds characterized by their capacity to elicit profound alterations in waking consciousness, comprising changes to mood, cognition, and self-referential awareness.[1] Preliminary evidence that compounds, such as psilocybin, are safe and efficacious treatments for neuropsychiatric disorders, such as major

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Received March 31, 2023; accepted May 10, 2023. doi:10.1002/cpt.2958

depressive disorder has fostered a renewed interest in their effects.[2]

Like other psychedelics (e.g., *d*-lysergic acid (LSD), mescaline, and *N,N*-dimethyltryptamine (DMT)), the effects of psilocin (the active metabolite of psilocybin) are understood to be primarily mediated via partial serotonin (5-HT) receptor agonism, predominantly the 5-HT_{2A} receptor as well as 5-HT_{1A} and 5-HT_{2C} receptors.[3,4] Extensive human behavioral studies have characterized the acute subjective, cognitive, and autonomic effects of psilocybin,[5–7] making it a valuable candidate for clinical study.

Although significant emphasis has been placed on the central role of 5-HT_{2A} receptor agonism in mediating alterations to waking consciousness,[8] classical psychedelics are suggested to hold subtly distinct pharmacodynamics. Indolealkylamines, such as the ergoline LSD or the tryptamines psilocybin and DMT, exhibit varying receptor binding selectivity and potency particularly in comparison to phenethylamines, such as mescaline, likely as a function of their structural (as)similarity.[9] Evidence has begun to emerge suggesting experiential differences may not only be explained by functional selectivity at the 5-HT_{2A} receptor but an entourage of receptor subclasses.[10]

With the advent of modern biochemistry, novel compounds distinct from their classical progenitors have readily appeared. Of these is the psychedelic entactogen 2,5-dimethoxy-4-bromophen ethylamine (2C-B), a first-generation synthetic analogue of mescaline isolated and publicized by Alexander Shulgin in 1974.[11] Belonging to the 2C-series of 2,4,5 trisubstituted phenethylamines, members share core methoxy functional groups at carbons 2 and 5, but differ in ligands at the fourth position on the phenyl ring (e.g., bromine in 2C-B or propyl in 2C-P).[12] Manifold increases in receptor efficacy and potency with respect to mescaline have been observed following such alterations in ligand positioning.[13] 2C-B shows high 5-HT_{2A}/5-HT_{2C} receptor selectivity and has been demonstrated to reliably elicit head twitch responses in rodents, a behavioral proxy of 5-HT_{2A} agonism.[14,15] In recent years, research has indicated secondary affinity at 5-HT_{2B}, 5-HT_{1A}, dopamine $D_{1/2/3}$, adrenergic $\alpha_{1/2}$, histamine H_1, and $TAAR_1$ receptors.[13] Notably, 2C-B shows parallels with 3, 4-methylenedioxymethamphetamine (MDMA) due to reuptake inhibition of the serotonin reuptake transporter (SERT) and, to a less extent, norepinephrine (NET) and dopamine reuptake transporters (DATs),[16] likely supplemented by monoamine oxidase inhibition.[17]

To date, 2C-B is the most frequently used novel psychedelic among recreational drug users[18] and serves as a structural reference point for the development of novel compounds.[19] A body of survey data and anecdotal reports highlight mild psychedelic effects typical of serotonergic hallucinogens, paired with feelings of euphoria and emotional openness akin to the entactogen MDMA.[20,21] Previous acute naturalistic observational studies have served to expand on the relative safety of 2C-B and evidenced greater speech emotionality, reductions of anger, and impairments in emotional recognition, partly corroborating reports of behavioral profile distinct to classical psychedelics.[22,23] However, a complete neuropsychopharmacological assessment of its acute effects under double-blind conditions has yet to be performed.

The present study therefore sought to describe and compare the subjective, cognitive, and cardiovascular effects of 2C-B (20 mg) vs. psilocybin (15 mg) in healthy volunteers. Comparative studies using doses eliciting similar levels of subjective high (doses of psychotropic "equivalence") and using a within-subject design, such as those presented herein, offer the opportunity to directly assess commonalities between substances across a range of standardized measures. Moreover, by including an active comparator of comparable phenomenology and duration, such as psilocybin, it may also be possible to minimize expectancy effects clouding subjective responses to psychedelics.[1,24] Considering prior findings of entactogenic qualities,[23] we hypothesized 2C-B would produce distinct emotional effects compared with psilocybin.

MATERIALS AND METHODS

This study used a double-blind, placebo-controlled, crossover design with 3 acute experimental sessions to investigate responses to placebo, 2C-B, and psilocybin. Participants were randomly allocated to intervention orders following Latin-square counterbalancing. Acute sessions were separated by a 14-day interval as to minimize carryover effects and ensure drug washout.

The study (trial register NL8813) was conducted according to the Declaration of Helsinki (1964) and amended in Fortaleza (Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and was approved (NL73539.068.20) by the Academic Hospital and University's Medical Ethics committee of Maastricht University.

Participants

Twenty-two healthy participants (11 women) aged 19–35 years (mean ± SD: 25 ± 4 years) were recruited by word of mouth and advertisement shared via Maastricht University social media platforms. An overview of the inclusion criteria, CONSORT flowchart and complete demographic data can be found in the **Supplementary Materials**.

Study procedures

Participants were informed prior to the study they were to receive 20 mg 2C-B, 15 mg psilocybin, or placebo on 3 separate occasions. Each intervention was administered orally, in a closed cup either containing 200 mL of the vehicle bitter lemon (a bittering agent, placebo) or bitter lemon and psilocybin/2C-B (powder) to mask any potential taste. Blinding integrity was assessed retrospectively at the end of each experimental visit. Doses of psilocybin and 2C-B were chosen based on their psychotropic equivalence as defined by subjective drug high extrapolated from prior study data. Descriptions of dose selection, drug purchase, and laboratory visits are provided in the **Supplementary Materials**.

Subjective effects

Descriptions of all inventories are provided in the **Supplementary Materials**.

Subjective effects were assessed repeatedly using the visual analogue scales (VAS) at baseline (0 hours), +0.5, +1, +1.5, +2, +3, +4, +5, and +6 hours after administration. These scales included "*any drug effect*," "*good drug effect*," "*bad drug effect*," "*drug liking*," "*drug high*," "*happy*," "*concentration*," "*creative*," "*productive*", and "*sociable*" marked from "*not at all*" (0) to "*extremely*" (100) and "*sense of time*" marked from "*slow*" (0) to "*fast*" (100). The duration of acute subjective effects was estimated using the VAS "*any drug effect*" and extrapolating an on/off cutoff of 10% of the maximum individual response.

Hourly measures (0, +1, + 2, +3, +4, +5, and +6 hours) were taken for a broader characterization of present-state effects. Changes in mood were assessed using the 65-item Profile of Mood States (POMS) scale.

Levels of dissociative symptomatology were examined using the 19-item Clinician-Administered Dissociative States Scale (CADSS). Acute psychedelic effects were characterized using the 13-item Bowdle Visual Analogue Scale (BVAS). Last, current and general levels of drug liking and wanting were assessed using the 4-item Sensitivity to Drug Reinforcement Questionnaire (SDRQ).

Furthermore, participants completed retrospective measures at the end of each test day. Alterations in waking consciousness were assessed using the 94-item 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) and the Hallucinogen Rating Scale (HRS). In addition, levels of subjective ego-dissolution as defined by the 8-item Ego Dissolution Inventory (EDI) and end of session changes in trait empathy as per the 28-item Interpersonal Reactivity Index (IRI) were examined.

Cognitive tasks

A computer-based task battery was implemented during peak subjective effects to determine the differential impact of psilocybin and 2C-B on domains of cognition: Motor Control Task (MCT; sensorimotor coordination). Psychomotor Vigilance Task (PVT; sustained attention), Digit Symbol Substitution Test (DSST; overall cognitive impairment), Tower of London (TOL; executive functioning), the immediate and delayed (+30 minutes), Spatial Memory Test (SMT; spatial memory), the Matching Familiar Figures Test (MFFT; reflection impulsivity), and the Multifaceted Empathy Test (MET; cognitive and emotional empathy). Parallel versions of the DSST, TOL, SMT and MFFT were provided for each dosing day. Participants were refamiliarized with all instructions prior to each task. All tasks and outcome measures are described in detail in the **Supplementary Materials**.

Cardiovascular effects

Blood pressure and heart rate were assessed hourly (0, +1, + 2, +3, +4, +5, and +6 hours) with an arm blood pressure cuff (M6 Comfort Model HEM-7360-E; Omron-Healthcare, Kyoto Japan). For each timepoint, rate pressure product (systolic blood pressure * heart rate) was calculated as a measure of hemodynamic workload.

Pharmacokinetic assessments

Venous blood samples were taken hourly (0, +1, + 2, +3, +4, +5, and +6 hours) to assess levels of serum psilocin and 2C-B (ng/mL) using liquid chromatography–tandem mass spectrometry (Agilent, Waldbronn, Germany). Noncompartmental areas under the curve (AUCs) and half-lives were extrapolated (see **Supplementary Material**).

Statistics

We first determined peak changes from baseline for all repeated measurements (ΔE_{max} and/or ΔE_{min}). Baseline-adjusted E_{max} scores were calculated for all cardiovascular measures to assess clinically significant changes. All outcomes were incorporated into Linear Mixed Models with drug condition as a main fixed effect and participant as a random intercept to account for the dependency between repeated measures. A first-order autoregressive covariance structure was used. If a significant main effect of drug condition was observed, estimated marginal means were compared between drug conditions. Tukey's method was used to correct for multiple comparisons in all analyses.

Statistical models were estimated using the *lme* function of the nlme (version 3.1.162) and the ImerTest (version 3.1.3) library within R (version 4.2.1). For all analyses, the alpha criterion was set at $P < 0.05$. Missing data and study power calculations are outlined in the **Supplementary Materials**. All statistics are summarized in **Tables S1–S4**, with all pairwise comparisons supplied in **Table S5**. Measures subject to a main effect of drug are reported in the text.

RESULTS

All 22 participants completed each condition of the study. Both 2C-B and psilocybin were well-tolerated, with no serious adverse events arising throughout the course of the study.

Subjective effects

Subjective effect VAS over time is shown in **Figure 1a**. Statistics are summarized in **Tables S1** and **S5**. Overall, 20 mg 2C-B and 15 mg psilocybin generated significant yet equivalent increases in scores across most measures of subjective drug intensity (any drug effect, good drug effect, drug liking, and drug high) in comparison to placebo. 2C-B produced significant elevations in bad drug effect compared with placebo, but not psilocybin. Subjective effects abated in under 6 hours for 86.3% of participants under 2C-B vs. 63.6% under psilocybin (**Figure 1b**, see **Supplementary Materials** for additional details).

The VAS pertaining to mood and time perception revealed further similarities. Both drugs significantly increased ratings of happiness and creativity in comparison to placebo with no differences arising between the two. Similarly, 2C-B and psilocybin equally induced greater mean reductions over time for self-reported sociability. Maximal reductions in concentration were significantly greater for psilocybin compared with placebo but not 2C-B. 2C-B and psilocybin similarly induced greater slowing of time perception in comparison to placebo, whereas increases in speed of time were significantly greater for psilocybin in comparison to 2C-B and placebo.

Multidimensional measures of mood, drug effects, and drug liking were taken hourly (see **Figure 2**, **Tables S1**, **S5**). Mood as assessed by the POMS (**Figure 2a**) revealed a greater degree of emotional lability under psilocybin. Psilocybin significantly increased levels across all negative mood subscales (total mood disturbance, tense, anger, fatigue, depression, and confusion) compared with placebo. Of these, levels of depression were also significantly greater for psilocybin than 2C-B. Conversely, 2C-B solely elicited significant increases for the tense and confusion subscales in comparison with placebo. 2C-B produced significant increases in markers of positive affect (vigor, elation, and friendliness) compared with placebo with the elevations in total positive mood of larger magnitude than under psilocybin. Both compounds generated comparable significant increases on SDRQ scales of current and general drug liking and wanting compared with placebo.

Altogether, neither substance significantly differed from one another on any multidimensional measures of acute drug effects. Subjective ratings of dissociation (**Figure 2b**) and their corresponding subfactors (depersonalization, derealization, and amnesia), as assessed by the CADSS, were significantly greater under both drugs than placebo. Similarly, real-time scores of internal perception and external perception and high as per the BVAS (**Figure 2c**) were significantly greater for both substances compared with placebo.

Figure 3 shows participant ratings on 3 retrospective questionnaires completed approximately 6 hours after drug administration. Statistics are summarized in **Tables S2** and **S5**. These results generally show significant increases in measures assessing

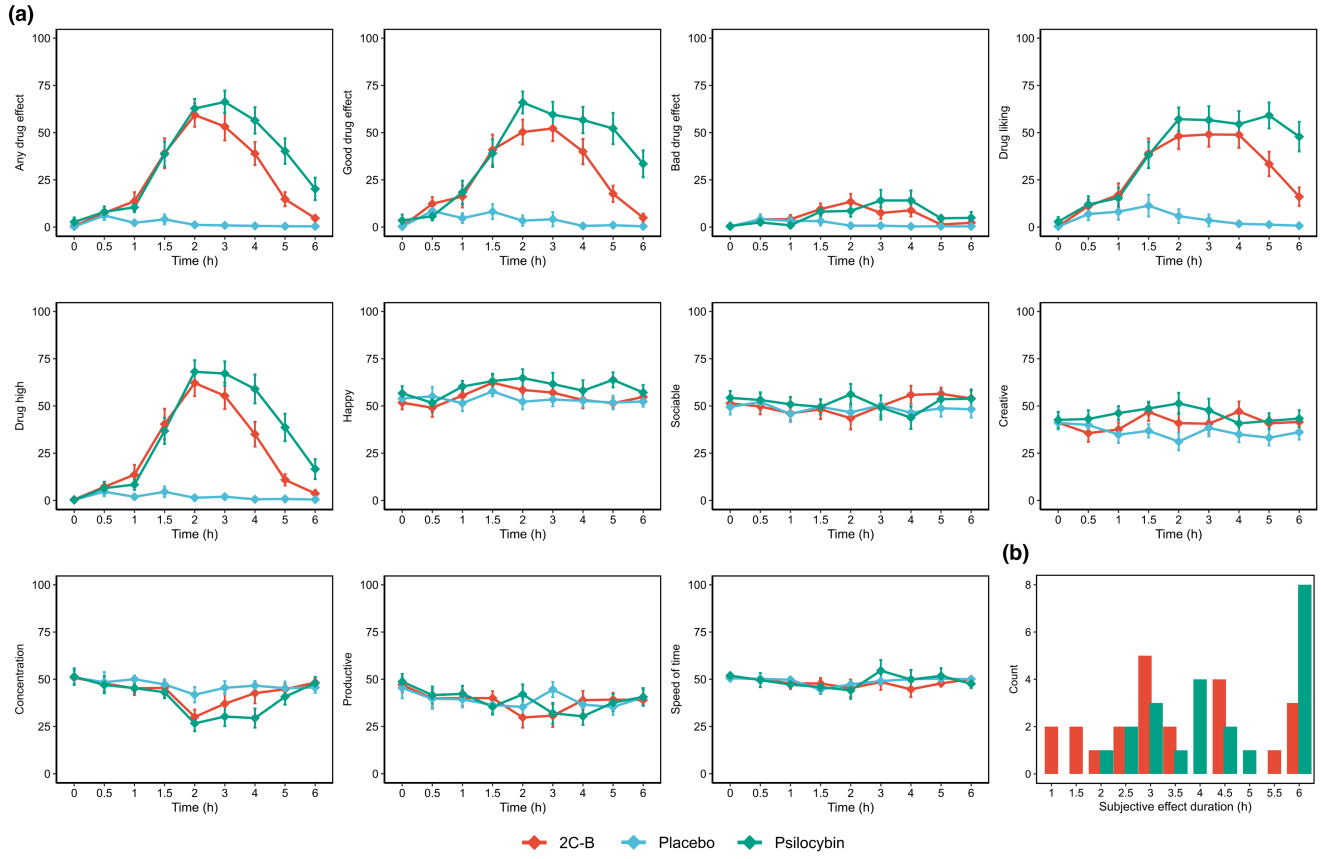

Figure 1 Subjective effects of 2,5-dimethoxy-4-bromophenethylamine (2C-B) and psilocybin over time on visual analogue scale (VAS) measurements of subjective effects. (**a**) Time courses of each VAS measurement. Data are presented as mean ± SEM (brackets). All values and corresponding pairwise statistics are presented in **Tables S1** and **S5**. (**b**) Count plot of *"Any effect"* on/off duration. Absolute frequencies for each bin are depicted for each drug.

alterations to waking consciousness after 2C-B and psilocybin. On the 5D-ASC, 2C-B elicited a total alteration in waking consciousness of less magnitude in comparison to psilocybin (**Figure 3a**).

2C-B generated significantly greater effects for most scales in comparison to placebo, other than for auditory alterations, spiritual experience, and disembodiment. Psilocybin produced significant increases in all dimensions of the 5D-ASC in comparison to placebo. Particularly, psilocybin produced significantly greater increases in the scales oceanic boundlessness, anxious ego dissolution, auditory alterations, vigilance reduction, changed meaning of percepts, and impaired control and cognition than 2C-B. Both produced significantly greater increases on the EDI compared with placebo (**Figure 3a**). On the HRS, 2C-B and psilocybin produced significant increases in 4/5 dimensions other than volition (**Figure 3b**). Notably, psilocybin produced significantly greater increases on the affect and cognition scales than 2C-B. Neither substance significantly differed on the intensity scale of the HRS. Last, neither compound elicited any clear immediate changes to trait empathy relative to placebo, as indexed by the IRI (**Figure 3c**).

Neuropsychological task battery

Altogether, on all cognitive outcome measures, 2C-B and psilocybin produced comparable effects (see **Figure 4**, **Tables S3**, **S5**). Both produced significant impairments in global cognitive function when compared with placebo, as indicated by a reduced number of correct responses and attempts on the DSST. However, no significant effect on general accuracy was identified.

Regarding local facets of cognition, both drugs relative to placebo were associated with significantly diminished scores in immediate and delayed SMT recall. Analyses revealed sensorimotor coordination, mental planning, reflection impulsivity, and empathy (cognitive and emotional) were unaltered under 2C-B and psilocybin, as indicated by the absence of a main effect of drug condition for the MCT, PVT, TOL, MFFT, and MET (+270 minutes, see **Supplementary Materials**), respectively. Delayed reaction times in comparison to placebo were selectively present for the DSST and TOL for both drugs as well as the PVT for psilocybin.

Cardiovascular effects

Acute effects on vital signs over time are shown in **Figure 5a**, with peak maximums shown in **Table S1**. For both compounds, significant pressor effects (systolic and diastolic) were observed in comparison to placebo. Systolic hypertension (> 140 mmHg) was observed under 2C-B ($n = 5$), psilocybin ($n = 8$), and placebo ($n = 2$), respectively. However, despite a main effect of drug, no clear significant differences in heart rate were observed. Whereas 2C-B produced a

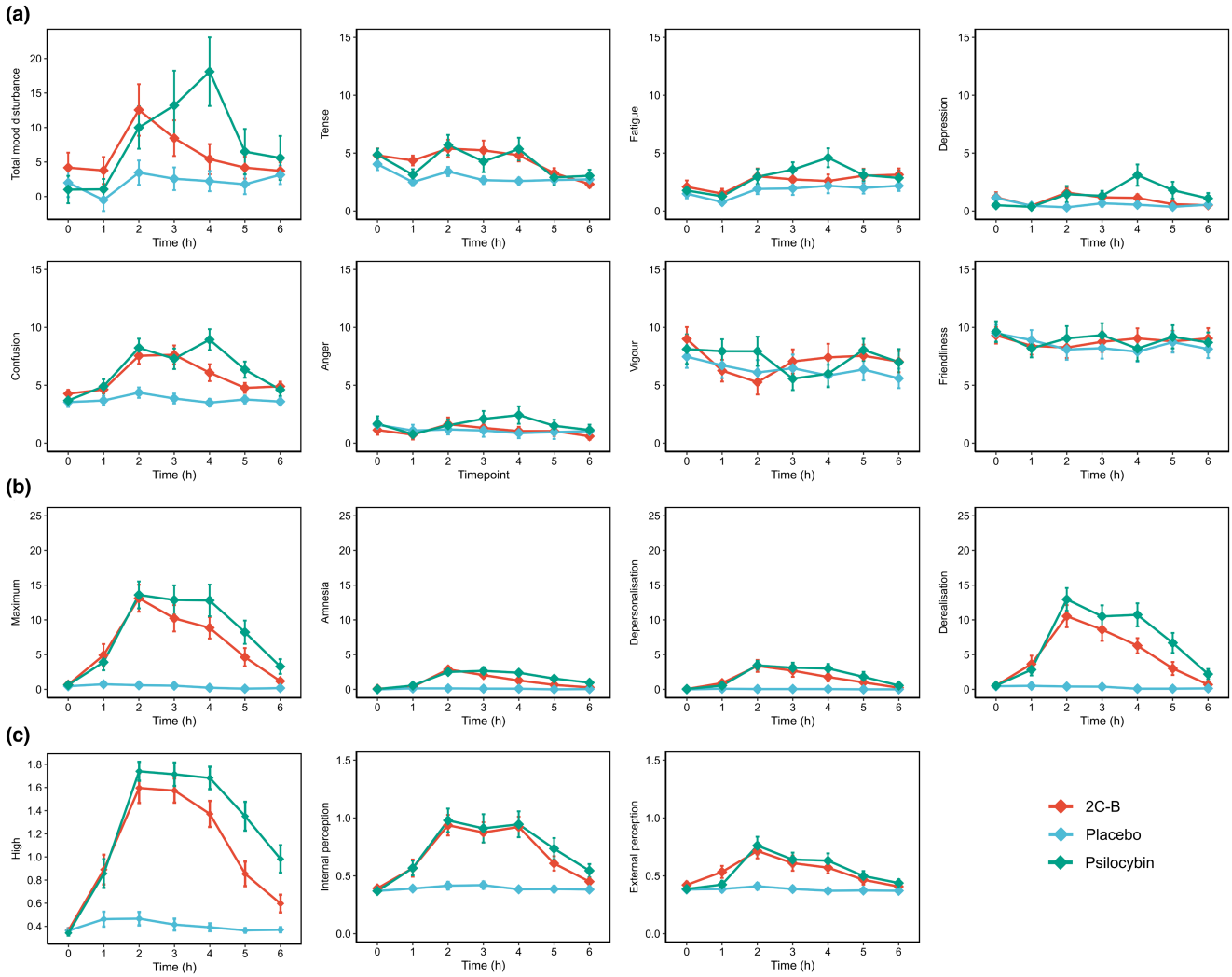

Figure 2 Effect of 2,5-dimethoxy-4-bromophenethylamine (2C-B) and psilocybin over time on hourly multidimensional measurements of mood, dissociation, and psychedelic effects. Data points are shown as means ± SEM (brackets). Corresponding pairwise statistics for these findings as well as additional subscales are presented in **Tables S1** and **S5**. (**a**) Time courses of all primary Profile of Mood States (POMS) dimensions. (**b**) Time courses of each Clinician-Administered Dissociative States Scale (CADSS) dimension. (**c**) Time courses of each Bowdle Visual Analogue Scale (B-VAS) dimension.

significantly greater rate pressure product in comparison to placebo, this did not significantly differ between our active conditions, suggesting an overall similar myocardial output.

Pharmacokinetics

Concentration time-curves can be found in **Figure 5b**. The maximum mean values (range, *n*) for 2C-B and psilocin serum concentrations (C_{max}) were 3.31 (1.63–7.58, $n = 21$) and 10.81 (5.26–25.47, $n = 21$) ng/mL, respectively, and concordant with applied oral doses.[5,22] Maximum serum concentrations peaked for 2C-B on average at 2.43 hours (1–4, $n = 21$) vs. 3.71 hours (2–5, $n = 21$) for psilocin. Mean AUC_{0-6h} values were 9.43 hours ng/mL (5.03–16.7, $n = 21$) for 2C-B and 33 hours ng/mL (21.7–71.6, $n = 21$) for psilocin. Available mean corresponding half-lives were 1.43 hours (1.02–2.46, $n = 17$) and 2.24 hours (1.44–3.81, $n = 7$) for 2C-B and psilocybin, respectively. For either drug, exploratory Spearman rank correlations did not reveal significant relationships among C_{max}, age, sex, nor weight (see **Supplementary Materials**).

Blinding

Following the completion of each test day, subjects were asked to retrospectively identify the intervention in question. Placebo was correctly identified by 95.5% of subjects, with 2C-B and psilocybin correctly identified by 63.6% of participants. 2C-B was misidentified as psilocybin by 36.4% of subjects. Psilocybin was misclassified as 2C-B for 31.8% of subjects and placebo for 4.5% of subjects ($n = 1$). Data pertaining to blinding and decision confidence are shown in the matrix S4.

DISCUSSION

The results presented herein provide the first clinical assessment and within-subject comparison of 2C-B and psilocybin across acute markers of subjective, cognitive, and cardiovascular effects

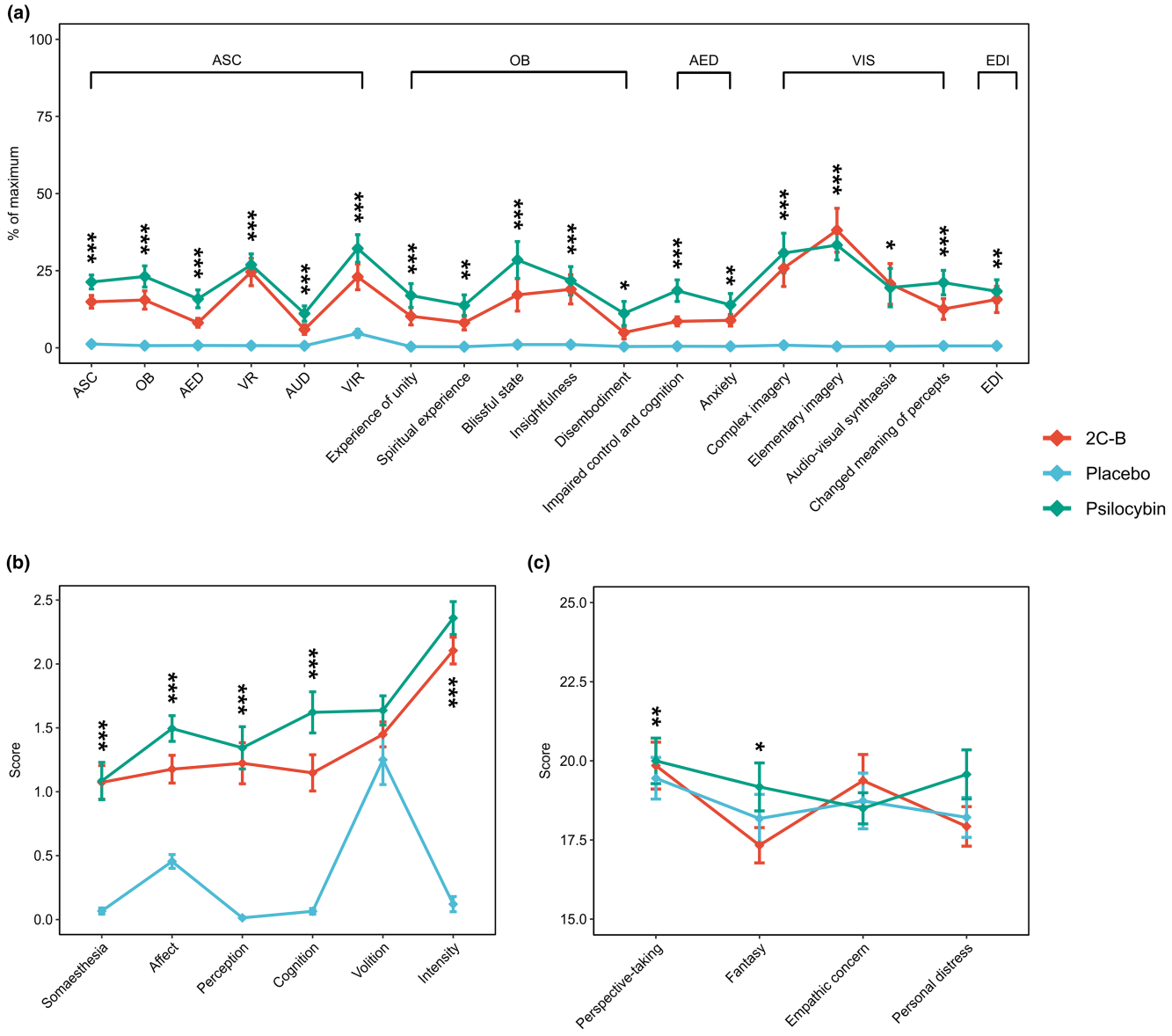

Figure 3 Effect of 2,5-dimethoxy-4-bromophenethylamine (2C-B) and psilocybin on retrospective measures of changes to waking consciousness and trait empathy. All means ± SEM (brackets) as well as corresponding pairwise statistics are presented in **Tables S2** and **S5**. The presence of significant main drug effect is indicated as follows: *$P<0.05$, **$P<0.01$, ***$P<0.001$. (**a**) Combined scores of the 5-Dimensions of Altered States Questionnaire (5D-ASC) alongside the Ego dissolution Inventory (EDI). (**b**) Participant ratings on the Hallucinogen Rating scale (HRS). (**c**) End-of-session differences in trait empathy on the interpersonal reactivity index (IRI). AED, anxious ego dissolution; OB, oceanic boundlessness; VIS, visual restructuralisation VR, vigilance reduction.

in a placebo-controlled fashion. Our results indicate fixed doses of 20 mg 2C-B and 15 mg psilocybin produce broadly similar increases in all acute ratings of peak drug effect intensity, comparable with prior dose-effect studies,[22,25] reflecting a psychotropic equivalence. In contrast, retrospective measures reflected alterations in waking consciousness of less experiential depth than psilocybin despite comparable cognitive impairment and cardiovascular stimulation.

Globally, 2C-B produced a range of subjective effects consistent with classical psychedelics.[1] Acute elevations in feelings of dissociation, perceptual change, creativity, and alterations to time perception were observed for both 2C-B and psilocybin. In contrast, nuanced differences in phenomenology were observed across retrospective measurements. Whereas 2C-B was found to elicit significant elevations across most scales outside of auditory alterations, disembodiment, and spiritual experience, the overall magnitude of alterations to waking consciousness (total 5D-ASC score) was markedly less than that of psilocybin. While exhibiting equivalent alterations to visual (e.g., external perception and visual restructuralisation) and bodily perception (ego dissolution, somaesthesia, and internal perception), participants under the influence of psilocybin reported a greater propensity for affective qualities of altered self-experience (e.g., oceanic boundlessness and anxious ego dissolution) as well as

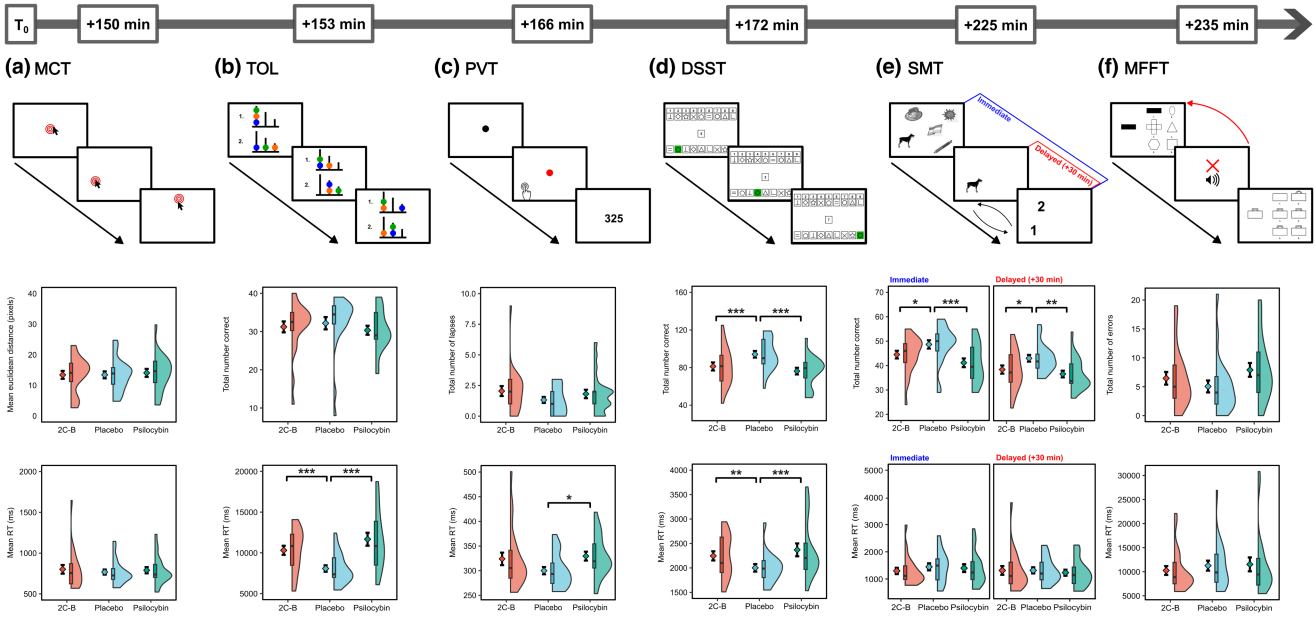

Figure 4 Approximate time course and primary outcomes of task battery. The uppermost panel of each column depicts a schematic of each task as presented to participants with each time of administration relative to dosing. Lower panels display outcomes as a combined violin plot, boxplot, and mean line (±SEM). In the boxplot, the line dividing the box represents the median, the ends represent the upper 75th/lower 25th percentiles, and the extreme lines represent the full range. Significant pairwise comparisons following a main effect of drug are indicated as follows: $*P<0.05$, $**P<0.01$, $***P<0.001$. (**a**) Motor control task. A target is presented randomly on screen and must be selected as quickly as possible. Participant accuracy (Euclidean distance from target center and response times (RTs) are recorded. (**b**) Tower of London (TOL). Participants must assess whether the end-arrangement (1 > 2) can be accomplished in two to five steps as quickly as possible. RTs and total correct responses are assessed. (**c**) Psychomotor vigilance task. Subjects must respond to a randomly appearing visual stimulus as quickly as possible. Total attentional lapses (RTs > 500 ms) and RTs are registered. (**d**) Digit Symbol Substitution Test (DSST). Participants must quickly match novel inputs according to their corresponding digit-symbol combination within 90 seconds, with total correct responses and RTs being the primary outcomes. (**e**) Spatial memory test. Participant must memorize the location of a sequence of 10 targets and individually indicate their correct position (1/2). Subjects are queried 30 minutes later on their location. Total correct responses and RTs are measured. (**f**) Matching familiar figures task. Targets must be matched to one of six possible corresponding alternatives as quickly as possible. Trials are repeated in the presence of an error, with main outcomes being the total number of errors and RTs. All outcomes and corresponding pairwise statistics are presented in **Tables S3** and **S5**. MCT, Motor Control Task; MFFT, Matching Familiar Figures Test; PVT, Psychomotor Vigilance Task; SMT, Spatial Memory Task.

impairment (e.g., vigilance reduction, impaired control and cognition). Together, these findings support descriptions of 2C-B being non-ego-threatening in nature, lacking the otherwise more serious headspace of classical precursors while imparting a greater emphasis on visual and tactile domains.[21] Similarly, 5D-ASC experiential depth has been shown to distinguish 2C-B from other novel indoleaklylamines.[18] Subtle pharmacodynamic differences between psilocybin and 2C-B may ultimately arise due to differing binding-profiles, given both the autoinhibitory and potentiating interplay of 5-HT_{1A}/5-HT_{2C} receptor subtypes on 5-HT_{2A}-mediated behavioral responses.[26] Alternatively, it can be suggested the brunt of experiential dissimilarities may instead lie in differing duration or dosage, given both 2C-B and psilocybin were unmasked marginally above chance by participants (63.6% of cases). Full substitution of 2C-X compounds with LSD or 2,5-Dimethoxy-4-iodoamphetamine has been previously shown[27] as well as limited discriminability between psilocybin and LSD in comparative studies.[25]

Whereas classical psychedelics and entactogens partly overlap in regard to their capacity to elicit a positive affective bias,[28] the former may hold a greater propensity to induce dysphoric reactions due to greater emotional lability. Per prior work,[22,23,25,29] significant elevations in measures pertaining to euphoria (e.g., drug liking, drug high, and good drug effect) and friendliness for both 2C-B and psilocybin in comparison to placebo were identified. However, subjects under psilocybin also showed sustained mood disturbance compared with placebo, with significantly larger increases in depression and overall greater emotional range (affect) than 2C-B. Furthermore, compared with placebo, 2C-B did not demonstrate significant elevations in most acute POMS markers of negative affect (anger, fatigue, and depression) instead producing elevations in vigor, elation, and positive mood in a similar manner to MDMA.[30] Seconding this, 2C-B's effects have been described to resemble a "candy flip," the concurrent use of MDMA and LSD.[21] By nature of their action as monoamine reuptake inhibitors, entactogens and psychostimulants are likely to confer less susceptibility to negative mood states. For example, noradrenergic effects appear important for their euphoriant nature,[31,32] whereas DAT/SERT selectivity has been suggested to distinguish amphetamine-like stimulants from entactogens.[33] In this regard, MDMA and 2C-B have been shown to hold similar DAT/SERT inhibition ratios of 0.08, whereas stimulants, such as methamphetamine show values greater than 10.[13] Pharmacological challenge studies using duloxetine (an SERT/NET reuptake inhibitor) and

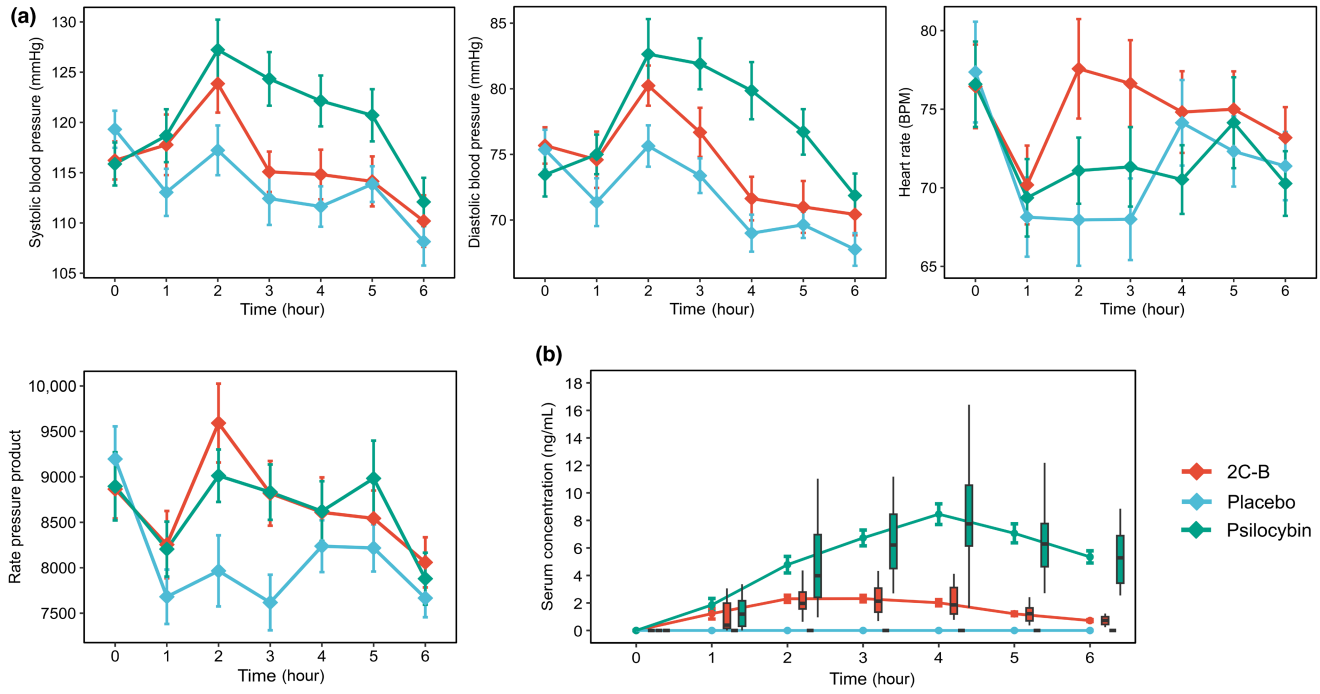

Figure 5 Cardiovascular and pharmacokinetic time-courses of 2,5-dimethoxy-4-bromophenethylamine (2C-B) and psilocybin. (**a**) Cardiovascular effects over time. Data points are shown as means ± SEM (brackets) with statistical outcomes provided in **Tables S1** and **S5**. (**b**) Pharmacokinetic time courses for 2C-B and psilocin. Data points are shown as means ± SEM (brackets) in conjunction with a boxplot for which line dividing the box represents the median, the ends represent the upper 75th/lower 25th percentiles, and the extreme lines represent the full range.

reboxetine (an NET reuptake inhibitor) seemingly abolish most mood-enhancing effects of MDMA.[32,34]

Overall, 2C-B and psilocybin produced a similar profile of cognitive impairment. For the DSST, both compounds yielded reductions in the number of attempted and correct responses, with expectedly longer reaction times. However, neither substance exerted a significant effect on accuracy. Our observations are wholly congruent with work finding psilocybin dose-dependently reduces trial attempts yet spares global accuracy.[35] Although we agree with Barrett *et al.*'s 2018 interpretation that the absence of decrements in accuracy is unlikely to be indicative of global executive impairment, we propose parallel reductions in trial attempts and reaction time are another reflection of local impairment. Compensatory psychomotor slowing under high intrinsic cognitive load is likely indicative of deficits in information processing speed rather than a volitional shift in performance strategy[36] prioritizing accuracy over speed. There is also good evidence to suggest disruptions to temporal processing and sensorimotor gating are mediated by 5-HT_{2A} agonism.[37,38] Deficits in information processing may also consequently explain worsened TOL reaction times in the absence of any main effect on planning. General assessments of executive function, such as the DSST, are often reliant on a combination of latent cognitive processes, such as good motor coordination, spatial memory, sustained attention, and response inhibition all of which may be differentially affected according to dose or agent in question.[39] For example, motor coordination under psilocybin was only previously shown to be affected under high doses (20 mg and beyond).[35] We also observed significant impairments to both working and long-term spatial memory under each compound despite mixed evidence at moderate doses.[7,40] Furthermore, any attentional deficits induced by primary 5-HT_{2A} agonists are likely selective: studies using psilocybin in combination with ketanserin (a 5-$HT_{2A/2C}$ antagonist) have specified declines in attentional tracking ability on paradigms requiring distractor inhibition,[41] suggesting an enhanced salience of distractor stimuli rather than reduced sustained attentional capacity per se. Whereas disruptions in inhibitory motor responding are seemingly a core feature of serotonergic hallucinogens,[30,42] no effect on MFFT performance was identified, reflecting an unaffected impulsive choice capacity.[43] Similarly, no empathogenic qualities were identified on the MET for either drug, notwithstanding elevations in emotional empathy being cited for similar doses of psilocybin and MDMA.[44] With both tasks administered at the tail-end of effect intensity, any absence of effect may be a function of time. Going forward, homing in on clinically relevant cognitive control domains will specify our findings further. With alterations in cognitive flexibility being cited as a marker of the therapeutic effects of classical psychedelics, future use of set-shifting paradigms may highlight novel differences.[45]

Analogous elevations in blood pressure were identified under 2C-B and psilocybin in comparison to placebo. These were modest in nature and consistent with earlier trials using psilocybin or 2C-B.[6,22] Magnitudes of change were also appreciably less than those observed following the administration of MDMA and related amphetamines.[28] Despite heart rate being significantly less under psilocybin than 2C-B, no differences were observed

for 15 mg psilocybin relative to placebo, as previously described for similar doses[2,25,46] In addition, we did not replicate the prior finding of elevated heart rate under 2C-B,[22] likely as a result of differing subject inclusion criteria. Thus, given neither drug generated notable differences in relation to placebo, these preliminary findings therefore cautiously indicate that the 15 mg psilocybin and 20 mg 2C-B hold similar cardiovascular effects. However, it should be stressed that assessing the full range of 2C-B's autonomic and endocrine (e.g., cortisol) effects in future phase I trials may be more fruitful for assessing the tolerability of 2C-B.

The kinetics of 2C-B were largely dissociable from those of psilocin. Whereas both compounds demonstrated comparable onset times, the effects of 2C-B were shorter than those of psilocybin, mostly abating within 6 hours. This was mirrored by a shorter half-life and smaller AUC for 2C-B in comparison to psilocybin. These findings of low bioavailability may be in agreement with preclinical work suggesting that 2C-B undergoes extensive first-pass metabolism.[47] Body weight had no influence on 2C-B or psilocin serum concentrations, Thus, unlike MDMA administering 2C-B as a fixed dose may confer equivalent advantages to weight-adjusted dosing similarly to other classical psychedelics.[5,48]

Limitations inherent to the study design warrant consideration. Firstly, single doses were used. For a complete categorization of 2C-B, future trials (e.g., NCT05523401) using an escalating dosing regimen with both MDMA and psilocybin as comparators of interest may provide applicable dosing ranges for healthy subjects. Furthermore, all neurocognitive tasks were performed at fixed timepoints as to accommodate a battery of sufficient breadth. With psychoactive effects being timeline dependent, differences in actual vs. perceived impairment may be reliant on pharmacokinetic differences. However, most tasks were administered at times of approximate peak subjective effects, maintained across the 2 and 4-hour timepoints for both compounds. It is therefore likely that tasks administered at these timeframes were not compromised by differences in task timing relative to effect intensity ratings. The present study also had a primary focus on the immediate effects of each compound and by design, did not extend pharmacokinetic sampling beyond 6 hours. Given the subjective effects of psilocybin were not self-resolving by 6 hours, future studies spanning a full sampling interval may more accurately extrapolate population pharmacokinetic parameters, such as half-life, clearance, or half-maximal effective concentration. Last, testing was performed in a controlled environment, enrolling a homogeneous sample of experienced volunteers. Thus, subjects in different settings, pertaining to different backgrounds may respond in unseen ways to 2C-B or psilocybin.

Caveats aside, our findings highlight key considerations for clinical pathfinding. If shown to produce positive mood sequelae akin to classical precursors, future novel analogues, such as 2C-B, which might potentially elicit a mentally "clear" subjective state, are likely scalable to implement at a clinic, given that preparation time pertaining to dysphoria can be reduced. For example, evidence of a lessened predisposition to adverse psychological effects may make 2C-B a useful means by which patients apprehensive of macrodoses or at risk of adverse reactions (e.g., high neuroticism)[49] can be familiarized with a psychedelic-induced subjective experience within a therapeutic model, whereas retaining high resemblance to classical psychedelics in its capacity to induce ego dissolution. Accordingly, doses of 15-30 mg 2C-B have been reportedly employed in both individual and group psycholytic psychotherapy, often adjunct to MDMA or LSD.[50]

CONCLUSION

In summary, these findings give new impetus to the categorization of 2C-B as a psychedelic drug with some entactogenic properties. Producing a spectrum of acute subjective, cognitive, and pressor effects compatible with a primary 5-HT_{2A} mode of action, 2C-B produces an effect profile of intermediary experiential depth. Subsequently assessing its sub(acute) effects on brain functional organization and affective processing will be valuable for understanding its relative harms and clinical utility.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors thank Maria Balaet for providing the MCT, Emma de Brabander, Vitea Medici, Ajna Jansson, and Chantal Delaquis for assistance in conducting the study, and Cees van Leeuwen for providing medical supervision and screening.

FUNDING

J.G.R. acknowledges financial support from the Dutch Research Council (NWO, grant number 406.18. GO.019).

CONFLICT OF INTEREST

K.P.C.K. is a principal investigator on research projects, the present study not included, that are sponsored by Mindmed and MAPS, and is a paid member of the scientific advisory board of Clerkenwell Health. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

P.M. wrote the manuscript. P.M., N.L.M., E.L.T., K.P.C.K., and J.G.R. designed the research. P.M., N.L.M., J.T.R., and R.P. performed the research. P.M and S.R. analyzed the data. S.W.T. contributed new analytical tools.

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