

## RESEARCH ARTICLE

# The chemical induction of synaesthesia

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## Abstract

**Objective:** Preliminary research suggests that experiences resembling synaesthesia are frequently reported under the influence of a diverse range of chemical substances although the incidence, chemical specificity, and characteristics of these effects are poorly understood.

**Methods:** Here we surveyed recreational drug users and self-reported developmental synaesthetes regarding their use of 28 psychoactive drugs from 12 different drug classes and whether they had experienced synaesthesia under the influence of these substances.

**Results:** The drug class of tryptamines exhibited the highest incidence rates of drug-induced synaesthesia in controls and induction rates of novel forms of synaesthesia in developmental synaesthetes. Induction incidence rates in controls were strongly correlated with the corresponding induction and enhancement rates in developmental synaesthetes. In addition, the use of lysergic acid diethylamide (LSD) was the strongest predictor of drug-induced synaesthesia in both controls and developmental synaesthetes. Clear evidence was observed for a clustering of synaesthesia-induction rates as a function of drug class in both groups, denoting non-random incidence rates within drug classes. Sound-colour synaesthesia was the most commonly observed type of induced synaesthesia. Further analyses suggest the presence of synaesthesia-prone individuals, who were more likely to experience drug-induced synaesthesia with multiple drugs.

**Conclusions:** These data corroborate the hypothesized link between drug-induced synaesthesia and serotonergic activity, but also suggest the possibility of alternative neurochemical pathways involved in the induction of synaesthesia. They further imply that the induction and modulation of synaesthesia in controls and developmental synaesthetes share overlapping mechanisms and that certain individuals may be more susceptible to experiencing induced synaesthesia with different drugs.

## KEYWORDS

consciousness, dopamine, perception, psychedelics, serotonin

David P. Luke and Devin B. Terhune contributed equally to this work.

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## 1 | INTRODUCTION

Synaesthesia is a neurodevelopmental condition that occurs in 1%–4% of the population (Simner, 2019) in which different stimuli (*inducers*) will reliably and involuntarily elicit atypical secondary experiences (*concurrents*; Grossenbacher & Lovelace, 2001; for reviews, see Ward, 2013; Ward & Simner, 2020). For instance, the word *rain* may taste like blueberries, or the letter *A* may elicit the colour red. Accumulating evidence suggests that synaesthesia has a genetic basis (Tilot et al., 2018), although individual associations seem to be shaped mostly by environmental constraints in early development (Witthoft & Winawer, 2013) and remain highly automatic and consistent over time in adulthood (Eagleman et al., 2007; Rothen et al., 2013). Synaesthesia typically emerges in early stages of development (Simner et al., 2009), although there have been multiple reports of adult-onset cases following stroke, drug use, physical trauma, and neuropathology (Brogaard, 2013; Farina et al., 2017; Ro et al., 2007; Yanakieva et al., 2019).

A point of controversy is whether synaesthesia can be induced in non-synaesthetes (Luke & Terhune, 2013; Rothen et al., 2018). Multiple lines of evidence suggest that the behavioural and phenomenological characteristics of synaesthesia can be temporarily triggered through cognitive training, verbal suggestion, and drugs (Brogaard, 2013; Hartman & Hollister, 1963; Luke & Terhune, 2013; Simpson & McKellar, 1955; for reviews, see Deroy & Spence, 2013; Terhune et al., 2017). Drug-induced synaesthesia is of particular interest, as it can broaden our knowledge about the neurochemical bases of synaesthesia. Research indicates that synaesthesia can be temporarily experienced by non-synaesthetes through consumption of classic psychedelics such as the partial serotonin receptor agonist lysergic acid diethylamide (LSD; Luke & Terhune, 2013; Terhune et al., 2016). It has been proposed that excessive levels of serotonin, or serotonin agonists and partial agonists activating 5-HT<sub>2A</sub> receptors, in cortical neurons is a common mechanism shared by (at least some cases of) developmental, acquired and drug-induced synaesthesia (Brogaard, 2013). In particular, excessive levels of serotonin may trigger synaesthesia through a selective enhancement of cortical excitability in visual cortex (Brogaard, 2013), which is a feature of developmental synaesthesia (Terhune, Murray, et al., 2015) and observed in trained synaesthesia (Rothen et al., 2018), although not in at least one case of acquired synaesthesia (Lungu et al., 2020). A recent double-blind, placebo-controlled trial of LSD confirmed that it produces perceptual effects resembling synaesthesia, although the induced associations did not display consistency (Terhune et al., 2016). This suggests that inducer-concurrent consolidation over time is required for the manifestation of this defining feature of developmental synaesthesia (Yanakieva et al., 2019).

Despite the consistent implication of the serotonin system in drug-induced synaesthesia, there exist multiple outstanding questions regarding the neurochemical specificity of these effects. In particular, nearly all studies of drug-induced synaesthesia to date have been restricted to drugs targeting the serotonin system (Luke & Terhune, 2013), and thus it remains unknown whether other

neurochemicals play a role in drug-induced synaesthesia. In addition, some individuals may be prone to synaesthesia irrespective of the drug class; the prevalence of such *synaesthesia-prone individuals* is unknown. Finally, aside from anecdotal reports (Baron-Cohen et al., 1996; Brang & Ramachandran, 2008; Cytowic, 1995), it remains poorly understood how different drugs modulate developmental synaesthesia, whether they induce novel forms of synaesthesia and whether these effects occur through similar neurochemical mechanisms to drug-induced synaesthesia in controls.

The present study sought to better understand the frequency, specificity, and characteristics of drug-induced synaesthesia. In particular, we were interested in determining the incidence of drug-induced synaesthesia, clarifying whether induced synaesthesia is more common in particular drugs or drug classes, as suggested by previous research (Luke & Terhune, 2013), and the types of synaesthesia experienced under the influence of chemical substances. In addition, we explored how the consumption of chemical substances impacted developmental synaesthetes. Toward these ends, we surveyed recreational drug users and self-reported developmental synaesthetes regarding the frequency of their consumption of typical recreational drugs and the extent to which these substances elicited synaesthetic experiences.

## 2 | METHODS

### 2.1 | Participants

1568 participants were recruited through various channels (see Procedure) and started the survey, and 644 completed it (41%). In the completed sample, age ranged from 18 to 74 years ( $M_{\text{age}} = 30.0$ ,  $SD = 12.2$ ). Given the paucity of research on this topic, a formal statistical power analysis was not undertaken. The pre-specified sample size was set at a minimum of 300 non-synaesthetes and 100 synaesthetes to ensure sufficient power to detect weak effects. Data collection continued past these minimum sample sizes until a particular point in the academic year had been reached. Data were not inspected or analysed until after data collection had ceased in order to prevent optional stopping. Country of residence was listed as United States (53%), United Kingdom (17%), Canada (5%), Australia (3%), Germany (3%), Netherlands (2%), Sweden (2%), Norway (1%), with the remaining participants coming from 37 other countries (all less than 1%; with 1% unreported). In the completed sample, 457 individuals reported not having synaesthesia and were identified as controls (99 females, 352 males, 6 unreported; 18–68;  $M_{\text{age}} = 29.1$ ,  $SD = 12.1$ ) and 187 self-identified as synaesthetes (60 females, 124 males, 3 unreported; 18–74;  $M_{\text{age}} = 29.5$ ,  $SD = 12.4$ ). The proportion of the latter group is larger than that observed in the general population (Simner, 2019) because this group was explicitly targeted to ensure sufficient statistical power and thus this proportion should not be considered representative of the corresponding prevalence of synaesthesia in the general population. All participants provided informed consent in accordance with local ethical approval.

## 2.2 | Materials

A survey was used to gather demographic information and assess different features of drug-induced synaesthesia in controls and synaesthetes. The survey included items pertaining to demographic information (age, gender, education, country of residence) and developmental synaesthesia (whether they had synaesthesia, whether they had synaesthesia only during childhood, and whether any of their family members had synaesthesia). The survey next assessed the use (and frequency of use) of 28 typical psychoactive substances and whether they had experienced synaesthesia (and how frequently) whilst under the influence of those substances. Synaesthesia was defined as an “experience in which there is a blending of the senses, such as shapes having a particular taste, sounds having a particular shape, or numbers having a particular colour”. The survey included the option to specify synaesthesia types using a dual drill down list of  $27 \times 27$  (729) possible inducer-concurrent combinations. Control participants were asked if they had ever experienced synaesthesia in the absence of drugs and were given a chance to specify the context. In addition to the questions on drug-induced synaesthesia, for each consumed drug, developmental synaesthetes were queried as to whether the drug had enhanced or suppressed their developmental synaesthesia. Finally, all participants were asked if they had ever had “flashbacks” of drug-induced synaesthesia (re-experiencing of a drug-induced synaesthetic experience). The survey utilized skip logic enabling participants to only respond to items relevant to their experience.

## 2.3 | Procedure

Developmental synaesthetes and recreational drug users were recruited through online advertisements for a study about drug use that made no reference to a hypothesized association between drug use and synaesthesia. Potential participants were targeted in English language online drug user or synaesthesia forums and websites ([Erowid.org](https://www.ericrowid.org); UK Synaesthesia Association) and social media platforms (Facebook) over a 6-month period. The survey was hosted by Qualtrics (Qualtrics, Provo, UT) and took approximately 10–60 min to complete depending on one’s drug use history.

## 2.4 | Analyses

All data are publicly available here: <https://osf.io/x45yf/>. All analyses were two-tailed and were performed in MATLAB (v. 2017b, MathWorks, Natick, MA). In the analysis of induced synaesthesia types, three different reported types of induced synaesthesia that appeared to be highly unlikely based on the synaesthesia literature, or an error, were excluded from the analyses. Otherwise, no data transformations were performed. Pearson correlations were computed along with bootstrap 95% confidence intervals (bias-corrected and accelerated method; 10,000 samples; Efron, 1987). Drug-induced

synaesthesia enhancement rates among developmental synaesthetes were calculated by subtracting self-reported suppression rates from enhancement rates for the entire sample for each drug. For various analyses, drugs were clustered into 12 classes. For the purposes of this paper the class of drugs considered to be classic psychedelics (Nichols, 2016) consisted only of tryptamine-type drugs acting as 5HT-2A receptor agonists or partial agonists (LSD, N,N-dimethyl-tryptamine [DMT], psilocybin/psilocin and ayahuasca, which contains DMT), hereafter referred to as *tryptamines* (for a similar classification, see Sanz et al., 2018). Clustering of drug classes was assessed by computing a drug class incidence dissimilarity index. This measure was computed by dividing the absolute difference between the incidence rate of each member in each class and the median incidence rate by the median incidence rate, thereby providing a percentage difference from the median rate for the respective class, with smaller values reflecting greater similarity of incidence rates. We then computed the median incidence dissimilarity measure for all classes. To evaluate the statistical significance of dissimilarity measures, we randomly permuted the data 10,000 times and computed the corresponding *p*-value of the observed dissimilarity index in the permutation distribution.

The strongest predictors of drug-induced synaesthesia were computed using four exploratory stepwise logistic regression analyses with the (binary) experience of drug-induced synaesthesia as the outcome variable. The analyses included either binary drug use or frequency of drug use for the 28 drugs in controls and developmental synaesthetes separately. For each analysis, we report Nagelkerke  $R^2$  as an estimate of the approximate percentage of variance in the outcome explained by the retained predictors. In order to assess the internal replicability of these exploratory effects, we used Bootstrap resampling (1000 samples) and we report the proportion of samples for which significant predictors were retained in the model (e.g., Wesselink et al., 2019). In order to estimate participants’ propensity for experiencing drug-induced synaesthesia, we computed a *synaesthesia-proneness* (SP) score:

$$SP = \frac{\sum_{i=0}^n (fs_d * (1 - ir_d))}{n}$$

where  $n$  is the number of drugs taken by an individual;  $fs$  is the self-reported frequency of induced synaesthesia on a drug  $d$ ;  $ir$  is the incidence rate of synaesthesia on a drug in the total sample; i.e., the relative proportion of participants reporting induced synaesthesia for that drug; and  $d$  is an arbitrary drug (of the set of 28). As can be seen, for each drug, frequency of induced synaesthesia for the drug is adjusted according to the inverse of the incidence rate based on the assumption that synaesthesia-prone individuals are those who will experience synaesthesia with a range of drugs and not only those with high induction incidence rates. This adjusted frequency is then averaged for all drugs that a participant has taken. We compared controls and developmental synaesthetes on SP scores and binary synaesthesia-induction (across all drugs) using *t*-tests and Fisher’s exact tests, respectively.

### 3 | RESULTS

#### 3.1 | Effects of recreational drugs on controls and developmental synaesthetes

Controls self-reported greater use of 19 of 28 drugs relative to synaesthetes, although the relative discrepancies between incidence rates tended to be minor (Figure 1). The high incidence rates for the different indexed drugs are likely an artefact of our recruitment procedure and should not be interpreted as representative of the general population. Controls and synaesthetes reported experiencing synaesthesia under the influence of a wide range of drugs. Most notable were the high incidence of synaesthesia among controls under the influence of LSD (57%), ayahuasca (49%), and psilocybin (45%), with a median incidence rate across all drugs of 15% (95% CI: 3, 25) in controls. In contrast, 0% of controls reported having experienced synaesthesia in other (non-drug) contexts. The incidence rates of induced synaesthesia for the 28 drugs did not significantly correlate with the corresponding incidence rate of usage,  $r = 0.01$ ,  $p = 0.96$  (95% CI:  $-0.37, 0.43$ ). Synaesthetes had numerically higher incidence rates across all drugs (Med: 23% [9, 38]) except 2C-B and *Amanita muscaria*. Induction of novel synaesthasias outside of the context of drug use was similarly rare: 2% reported experiencing synaesthesia whilst meditating. As in the controls, the incidence rates for induced synaesthesia and the rates of usage for the 28 drugs did not significantly correlate,  $r = 0.09$ ,  $p = 0.64$  (95% CI:  $-0.30, 0.51$ ).

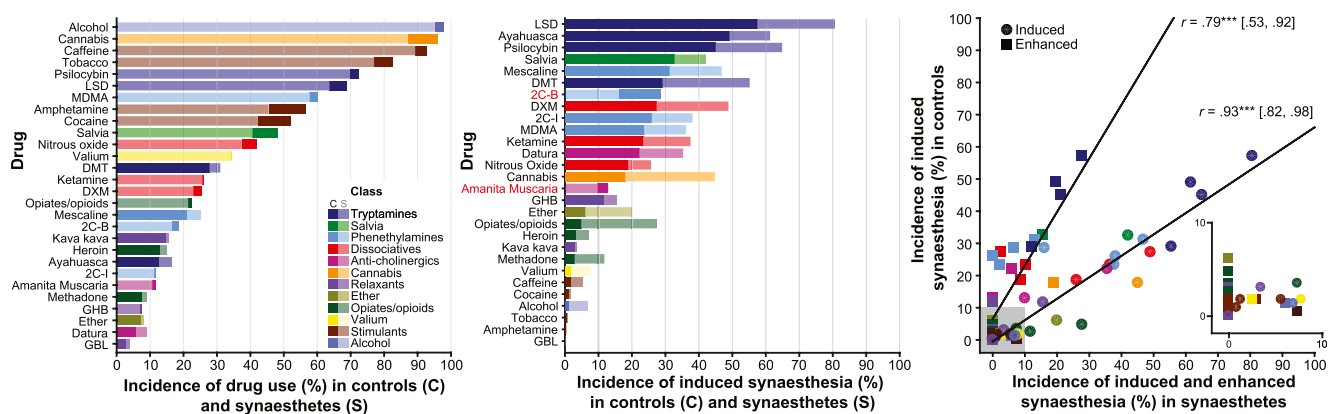
Notably, incidence rates for drug-induced synaesthesia across drugs were highly correlated across the two groups,  $r = 0.79$ ,  $p < 0.001$  (Figure 1). Similarly, incidence rates in controls correlated with *enhancement rates* of extant developmental synaesthasias in synaesthetes,  $r = 0.93$ ,  $p < 0.001$ . Finally, among synaesthetes, incidence rates of induced synaesthesia were strongly correlated with

enhancement rates,  $r = 0.78$ ,  $p < 0.001$  (95% CI: 0.51, 0.91). Among controls, 24% reported having flashbacks of drug-induced synaesthesia whereas 43% of synaesthetes reported such experiences,  $\chi^2(1) = 22.08$ ,  $p < 0.001$ ,  $\phi = 0.19$ . Cumulatively, these results suggest that induced synaesthesia varies considerably across drugs and that the same drugs that seem to induce synaesthesia in controls also appear to induce *novel* synaesthasias and *enhance* extant synaesthasias in developmental synaesthetes.

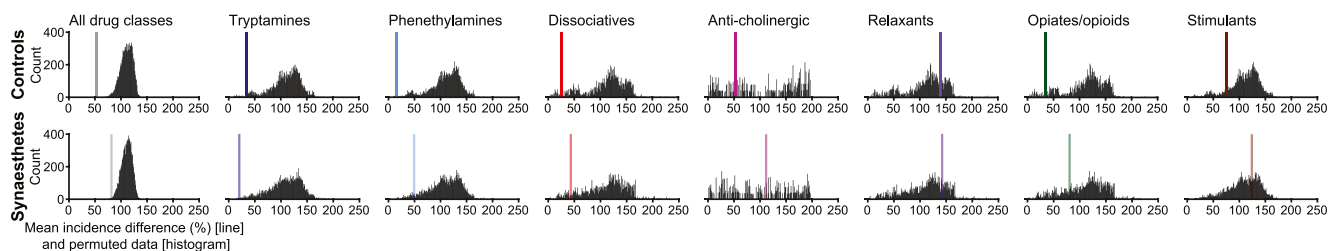
#### 3.2 | Clustering of drug-induced synaesthesia by drug class

A striking feature of the incidence rates of induced synaesthesia in Figure 1 is that drugs from the same classes appear to be characterized by similar induction report rates, suggesting intra-class clustering. For example, the four tryptamines surveyed were among the top 6 drugs for incidence rates of the 28 drugs in controls and comprised the top 4 in synaesthetes. Similar clustering was apparent with phenethylamines, dissociatives, opioids, and stimulants. To examine if this apparent clustering deviates from chance, we computed within-class dissimilarity indices for the incidence rates in the seven drug classes that were represented with two or more different drugs, thus excluding salvia (*Salvia divinorum*), cannabis, ether, Valium (diazepam), and alcohol (see Section 2).

The mean value across the seven drug classes among controls was 54%, which indicates that members of a drug class tended to be within 54% of the median incidence rate within the respective class. As can be seen in Figure 2, the incidence dissimilarity index value across drug classes among controls, 54% (95% CI: 33, 98), had a low probability of occurrence in the permutation distribution,  $M = 111\%$  (95% CI: 87, 130),  $p < 0.001$ . The same pattern was observed among



**FIGURE 1** Incidence of drug use and drug-induced synaesthesia in controls (C; non-transparent colours) and synaesthetes (S; transparent colours). Left: Incidence rates (%) for use of different drugs coloured by drug class. Middle: Incidence rates (%) for induced synaesthesia in the two groups as a function of drug and drug class. Drugs labelled in red denote higher incidence rates for controls than synaesthetes. Right: Incidence rates of induced synaesthesia across drugs among controls correlate with induction incidence rates (circles) and enhancement rates (squares) across drugs among synaesthetes. Rates in the 0%–10% range (grey region) are re-presented in the inset on the right. DMT, N,N-Dimethyltryptamine; DXM, dextromethorphan; GBL, gamma-Butyrolactone; GHB, gamma-Hydroxybutyric acid; LSD, lysergic acid diethylamide; MDMA, 3,4-Methylenedioxymethamphetamine; 2C-B, 4-Bromo-2,5-dimethoxyphenethylamine; 2C-I, 2-(4-Iodo-2,5-dimethoxyphenyl)ethan-1-amine



**FIGURE 2** Clustering of drug-induced synaesthesia as a function of drug class. Coloured lines represent the mean within-drug class incidence difference (%) across 7 drug classes and each individual drug class in Controls (top) and Synaesthetes (bottom). Histograms represent the corresponding permuted mean incidence differences (10,000 samples)

synaesthetes, albeit to a lesser degree,  $M = 82\%$  (95% CI: 49, 113), and was statistically significant relative to the permutation distribution,  $M = 111\%$  (95% CI: 90, 129),  $p = 0.003$ . For individual drug classes among controls, three drugs had mean dissimilarity indices that were statistically significant, relative to permuted data: tryptamines: 33%,  $p = 0.017$ ; phenethylamines: 15%,  $p = 0.006$ ; and dissociatives: 25%,  $p = 0.036$ . By contrast, the other drugs were all non-significant (anti-cholinergics: 53%,  $p = 0.23$ ; relaxants: 140%,  $p = 0.76$ ; opiates/opioids: 35%,  $p = 0.057$ ; stimulants: 75%,  $p = 0.11$ ). These results were similar for individual drug classes among synaesthetes, with significant effects for tryptamines: 20%,  $p = 0.003$ ; and phenethylamines: 49%,  $p = 0.048$ , albeit not for dissociatives: 43%,  $p = 0.072$ . As in the controls, indices did not significantly differ from permuted data for the other classes: anti-cholinergics: 112%,  $p = 0.45$ ; relaxants: 142%,  $p = 0.77$ ; opiates/opioids: 81%,  $p = 0.24$ ; and stimulants: 124%,  $p = 0.63$ . These results strongly suggest that the observed clustering of incidence rates within drug classes is unlikely to be random, particularly for tryptamines, and phenethylamines in both groups, and dissociatives in controls. These data seem to reflect a relatively similar incidence rate for induced synaesthesia based on the unique neurochemical impact of different drug classes.

### 3.3 | Predicting the occurrence of drug-induced synaesthesia

Our next set of analyses sought to examine whether drug-induced synaesthesia can be predicted on the basis of drug use (Table 1). Toward this end, we conducted four binary logistic regression analyses in which the outcome variable was drug-induced synaesthesia, treated as a binary variable collapsed across all drug classes. Separately for controls and synaesthetes, we performed two analyses including either binary drug use or frequency of drug use for each of the 28 drugs as predictors of the binary chemical induction of synaesthesia (having experienced drug-induced synaesthesia at least once or not).

The first analysis with the predictor set of binary drug use in controls was significant,  $\chi^2(6) = 70.48$ ,  $p < 0.001$ , accounting for approximately 20% of the variance. The model retained six significant predictors in the final step, each representing a distinct drug class. The mean of this distribution was  $R^2 = 0.26$  (0.16, 0.36) with three of the predictors (LSD, Ecstasy, and methadone) retained in 75% or more of the Bootstrap samples. The model including frequency of

drug use was also significant,  $\chi^2(5) = 48$ ,  $p < 0.001$ , accounting for slightly less variance,  $R^2 = 0.14$ . The final model retained five predictors, mean  $R^2 = 0.21$  [95% CI: 0.12, 0.31], with two (methadone and kava kava *Piper methysticum*) retained in 70% or more of the analyses. Notably, four predictors (LSD, *Amanita muscaria*, methadone, and kava kava) were retained in the final model for both analyses. Among synaesthetes, the model for binary drug use was significant,  $\chi^2(5) = 85.7$ ,  $p < 0.001$ , accounting for a substantially larger proportion of the variance,  $R^2 = 0.60$ . The final model retained four significant predictors, mean  $R^2 = 0.79$  (95% CI: 0.57, 0.98), with two (psilocybin and gamma-Butyrolactone [GBL]) retained in 70% or more of the analyses. Notably, GBL use was a replicable negative predictor of drug-induced synaesthesia. Finally, for the model including frequency of drug use as predictors was significant,  $\chi^2(5) = 90.2$ ,  $p < 0.001$ , accounting for a similar amount of variance,  $R^2 = 0.60$ . The final model retained four significant predictors, mean  $R^2 = 0.80$  (95% CI: 0.63, 1.00), with three (LSD, cannabis and dextromethorphan [DXM]) retained in 70% or more of the analyses. Interestingly, only two predictors (LSD and DXM) were replicable across both analyses in synaesthetes. Binary use and frequency of use for LSD were the only consistent predictors of drug-induced synaesthesia across the four analyses although these variables did not reliably exhibit strong replication rates. Other potentially notable patterns include the findings that *Amanita*, methadone and kava kava were replicable predictors across both analyses in controls. However, only methadone exhibited high replication rates in both models. By contrast, DXM was a replicable predictor in both analyses among synaesthetes with relatively high rates of replicability. It is particularly noteworthy that other than LSD, no drugs were replicable predictors across synaesthetes and non-synaesthetes in any of the analyses. Cumulatively, these results suggest that drug use can be used to reliably predict drug-induced synaesthetic experiences, with the most robust predictor across groups being LSD and other predictors including methadone in controls and DXM in synaesthetes.

### 3.4 | Types of drug-induced synaesthesia

Sound-colour, sound-space, and sound-shape were the three most commonly-reported forms of drug-induced synaesthesia. A notable result was the report of grapheme-colour synaesthesia, which is among the most widely studied forms of developmental synaesthesia

**TABLE 1** Coefficients for retained predictors (binary drug use for 28 drugs) in four stepwise logistic regressions on the chemical induction of synaesthesia in controls ( $N = 457$ ) and developmental synaesthetes ( $N = 187$ )

Predictors	Outcome measures															
	Controls								Synaesthetes							
	Binary use				Frequency of use				Binary use				Frequency of use			
	B	SE	<i>p</i>	BR (%)	B	SE	<i>p</i>	BR (%)	B	SE	<i>p</i>	BR (%)	B	SE	<i>p</i>	BR (%)
LSD	1.01	0.24	<0.001	95	1.06	0.50	0.04	58	1.95	0.72	0.007	56	7.71	2.46	0.001	77
Amanita	0.88	0.42	0.035	47	1.12	0.52	0.03	44								
Ecstasy	0.79	0.23	<0.001	83												
Psilocybin									1.64	0.66	0.01	82				
Cannabis													4.70	1.20	<0.001	92
Methadone	1.49	0.63	0.019	78	3.16	1.83	0.08	73								
Kava kava	0.70	0.35	0.049	49	2.67	1.14	0.02	72								
2C-B													-8.70	4.34	0.045	38
GHB					4.20	2.13	0.05	59								
GBL									-4.91	1.38	<0.001	89				
DXM									2.70	1.44	0.05	67	9.92	5.06	0.050	93
Valium	-0.65	0.24	0.008	61												

Note: Binary use and frequency of use for 28 drugs were included as predictors in separate regression models. Binary use, having used the drug or not (0/1); Frequency of use, how frequently the drug was used on a scale of 0-1 (with five possible values).

Abbreviations: BR, Bootstrap replications (out of 1000 resamples); DXM, dextromethorphan; GBL, gamma-Butyrolactone; GHB, gamma-Hydroxybutyric acid; 2C-B, 4-Bromo-2,5-dimethoxyphenethylamine.

but has not been widely reported in drug-induced synaesthesia (Luke & Terhune, 2013). We examined whether particular synaesthesia subtypes varied across drug classes. The cell counts for multiple drug classes were too low to allow for log-linear analyses, so we performed a series of chi-squared analyses contrasting the incidence of the 13 most common subtypes of synaesthesia across four different drug classes (Figure 3). The drug classes were found to differ only in the incidence of sound-colour synaesthesia,  $\chi^2(3) = 18.84$ ,  $p < 0.001$ ,  $\phi = 0.18$ . Subsidiary analyses revealed that tryptamines had a higher incidence rate than dissociatives,  $\chi^2(1) = 4.33$ ,  $p = 0.038$ ,  $\phi = 0.10$ , and salvia,  $\chi^2(1) = 16.04$ ,  $p < 0.001$ ,  $\phi = 0.19$ , and phenethylamines had a higher incidence rate than salvia,  $\chi^2(1) = 8.09$ ,  $p = 0.004$ ,  $\phi = 0.24$ , with all other effects being non-significant,  $\chi^2(1) < 2.7$ ,  $ps > 0.10$ ,  $\phi < 0.15$ . These results suggest firstly that sound-colour synaesthesia is the most common form of drug-induced synaesthesia, thereby corroborating previous results (Luke & Terhune, 2013; Terhune et al., 2016), and secondly, that the incidence of sound-colour synaesthesia scales with the differential induction rates across different drug classes. However, the results further suggest that types of induced synaesthesia do not seem to be specific to drug class.

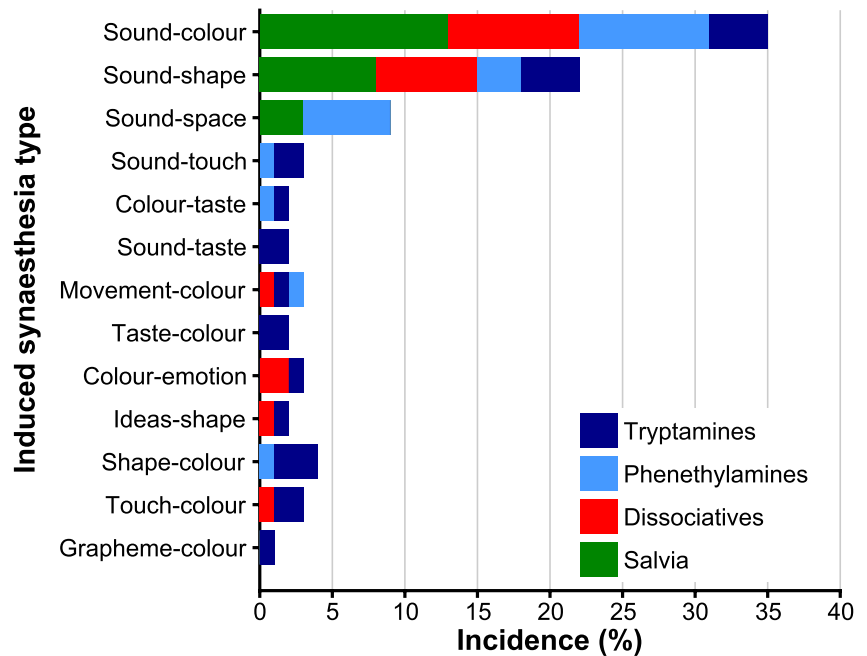
### 3.5 | Proneness to drug-induced synaesthesia

It is apparent that there is considerable variability in the incidence of drug-induced synaesthesia. In order to estimate the

prevalence of highly prone individuals, we calculated SP scores, which quantify an individual's tendency to experience drug-induced synaesthesia, taking into consideration the individual's drug use, whether they experienced synaesthesia for each drug, and the induction incidence for each drug in the sample (see Analysis section). We had aimed to evaluate whether SP among controls would be higher in those self-reporting as having had childhood synaesthesia or family members with synaesthesia; however, the incidence of these two subgroups was very low, five cases [1%] and eight cases [2%], respectively, and thus these data were not analysed further.

As can be seen in Figure 4, SP was heavily skewed in both controls and synaesthetes due to the relatively large proportions of the samples that had *not* experienced induced synaesthesia, 33% and 17%, respectively. Controls displayed lower binary induction rates (67%) than synaesthetes (83%), Fisher's exact  $p < 0.001$ ,  $\phi = 0.17$  (0.10, 0.24). Controls' SP scores ranged from 0 to 0.31,  $M = 0.05$  (95% CI: 0.040, 0.051), whereas those of synaesthetes' ranged from 0 to 0.43 in synaesthetes,  $M = 0.10$  (95% CI: 0.088, 0.115). This difference was also significant,  $t_{perm} = 8.90$ ,  $p < 0.001$ ,  $g = 0.77$  (95% CI: 0.58, 0.97). Both sets of results suggest that SP is greater in those self-reporting as developmental synaesthetes. We consider high SP as reflected in SP scores  $>3$  SDs above the respective mean of each sample (outliers), which corresponded to 24 controls (5%) and 11 synaesthetes (5%), which may reflect the relative proportions of individuals in these groups that are highly prone to induced synaesthesia.

**FIGURE 3** Incidence rates of different types of induced synaesthesia in controls as a function of drug class

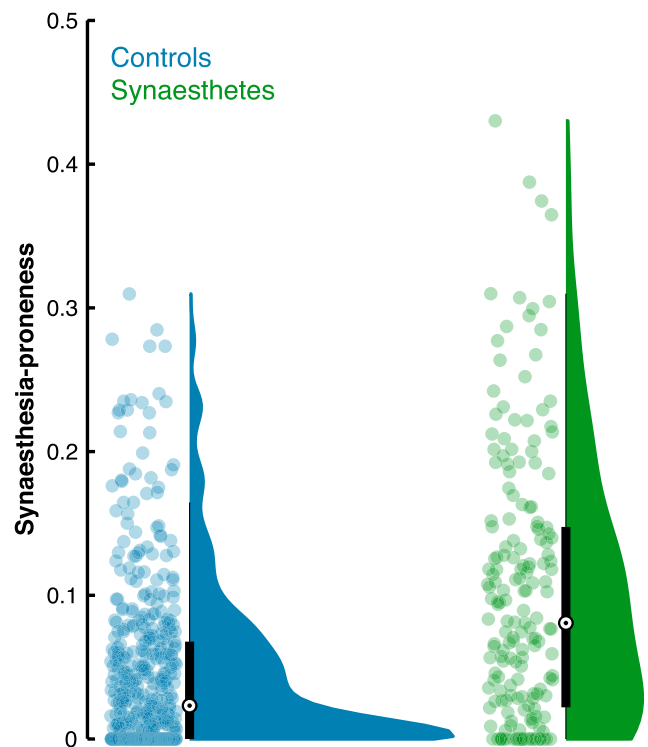


## 4 | DISCUSSION

Here we identified the incidence and characteristics of drug-induced synaesthesia in controls and the modulation of self-reported developmental synaesthesia across a range of recreational drugs. We corroborated the previously reported result that synaesthesia is commonly experienced following the consumption of classic psychedelics (e.g., LSD; Luke & Terhune, 2013), although multiple other drug classes were characterized by high incidence rates of induced synaesthesia (>20%) including phenethylamines, salvia, and dissociatives. Notably, we found clear evidence for within-drug class clustering of incidence rates; this strongly suggests that differential incidence rates across drug classes are non-random and thus attributable to differential neurochemical profiles. As in previous research (Hartman & Hollister, 1963; Luke & Terhune, 2013), sound-colour synaesthesia was the most common type of drug-induced synaesthesia. Our results also suggest that certain individuals are more susceptible to drug-induced synaesthesia than others. These results have implications for current understanding of induced synaesthesia, as well as the neurochemical bases of this condition and the neurochemistry underlying multisensory integration.

### 4.1 | Incidence and characteristics of drug-induced synaesthesia

Nearly all previous studies of drug-induced synaesthesia were restricted to LSD, mescaline, psilocybin, ayahuasca, or 3,4-Methylenedioxymethamphetamine (MDMA) (Luke & Terhune, 2013; Studerus et al., 2010). Since all of these act as (partial) serotonin receptor agonists, a persistent hypothesis in the literature is that they induce synesthesia-like experiences through activation of



**FIGURE 4** Synaesthesia-proneness frequency distributions in controls and synaesthetes. Markers, which are jittered along the x-axis to improve visualisation, denote individual participants, and smoothed histograms reflect kernel density estimates

5HT<sub>2A/2C</sub> serotonin receptors. Nevertheless, the non-serotonergic psychedelic substance *Salvia divinorum* (and its derivative savinorin A) was previously found to also induce synaesthesia (Addy, 2011; Babu et al., 2008; for a review, see Luke & Terhune, 2013). The present results corroborate both of these patterns.

Members of the drug class of tryptamines, which act primarily as (partial) 5HT-2A receptor agonists, were reliably characterized by the highest incidence rates. In addition, psychedelic phenethylamines, which also act primarily as (partial) serotonin receptor agonists (Nichols, 2016), had the third highest incidence rates (see below as well). However, similar to previous findings (Addy, 2011; Luke & Terhune, 2013), *Salvia divinorum* and dissociatives (e.g., ketamine), which do not seem to primarily act on serotonin receptors (Kapur & Seeman, 2002; Roth et al., 2000), were also characterized by high incidence rates. Rather, *salvia divinorum*, having the active molecule salvinorin A, seems to act *only* on kappa opioid receptors (Roth et al., 2000), stimulating them to inhibit the release of striatal dopamine, whereas dissociatives primarily act as NMDA receptor (uncompetitive) antagonists (Roth et al., 2000; Vollenweider & Geyer, 2001), but may have downstream effects convergent with 5-HT<sub>2a</sub> receptor agonists, such as increased glutamate release and neural excitation, leading to subjective experiences somewhat similar to classic psychedelics (Moghaddam et al., 1997; Nichols, 2004). Interestingly, we also found a high incidence rate for cannabis—which is known to only act on cannabinoid receptors—especially for developmental synaesthetes. Taken together, these findings suggest a more nuanced view than the simple attribution of spontaneous drug-induced synaesthesia to (partial) serotonin receptor agonists and seem to indicate that these induced experiences are not exclusively serotonergic.

A notable feature of the present results is that the same drug classes that were reported to elicit synaesthesia in controls also seem to be reliably associated with the induction of novel forms of synaesthesia and the modulation of existing forms in self-reported developmental synaesthetes. For example, tryptamines, phenethylamines, salvia, and dissociatives were characterized by high incidence rates for novel types of synaesthesia in controls and developmental synaesthetes, as well as the enhancement of existing synaesthasias in the latter group. Moreover, drugs that do not seem to reliably induce synaesthesia in non-synaesthetes, such as stimulants and opiates, also had little impact on the experience or modulation of synaesthesia in developmental synaesthetes. Overall, there were strong positive correlations between incidence rates of induced synaesthesia in controls and incidence and enhancement rates of synaesthesia in developmental synaesthetes. To our knowledge, there has not been any systematic research on the impact of recreational drugs on developmental synaesthesia although the present findings are consistent with previous reports of the enhancement of developmental synaesthesia with LSD (Cytowic & Eagleman, 2009), mescaline, and amyl nitrate (Cytowic, 1995), and its weak enhancement or inhibition with alcohol, tobacco, caffeine, and amphetamines (Cytowic, 1995; Cytowic & Eagleman, 2009; for a review, see Luke & Terhune, 2013). These results therefore suggest that the neural mechanisms underlying drug-induced synaesthesia may share some similarities in controls and developmental synaesthetes.

Although drug-induced synaesthesia was reported for an array of different drug classes, there seemed to be a clear pattern of induction rates within and across drug classes. In particular, we observed a

within-drug class clustering of incidence rates: for both controls and synaesthetes independently, incidence rates tended to be very similar *within* drug classes. Significant within-drug class clustering was observed across drug classes but also within the classes of tryptamines and phenethylamines for both groups whereas for dissociatives, the clustering was only significant in controls. For the remainder of the drugs, within-class clustering was non-significant, although due to the small number of drugs in each class, these non-significant results likely reflect Type II errors and should be interpreted cautiously. Taken together, these results suggest that the similarity of incidence rates within drug classes are non-random. This seems to indicate that different drug classes produce synaesthesia through different systems and thereby further implicate different neurochemical pathways in the induction of spontaneous synaesthesia.

A further notable finding of the present results is that we were able to reliably and significantly predict the experience of drug-induced synaesthesia on the basis of participants' drug use patterns. Drug use, measured dichotomously or by self-reported frequency, for the 28 drugs was able to account for a substantial amount of the variance in drug-induced synaesthesia. Although multiple drugs were retained in the exploratory regression analyses, LSD was the only replicable predictor across all four analyses in controls and synaesthetes. These results corroborate previous research highlighting LSD to be highly effective in inducing synaesthesia (Luke & Terhune, 2013; Terhune et al., 2016) and our observation that LSD is characterized by the highest incidence rates of drug-induced synaesthesia. Notably, this effect seems to be unrelated to the actual use rates of these different drugs, as drug use rates were not reliably correlated with induced synaesthesia rates. The greater predictive utility of drug use in synaesthetes is plausibly attributable to the overall higher induced synaesthesia incidence rates but this is unlikely to represent a significant confound as other drugs with high induction incidence rates were not reliable predictors (e.g., psilocybin). Although we highlighted the neurochemical heterogeneity of induced synaesthesia above, these findings suggest that serotonin seems to be the neurochemical most reliably implicated in drug-induced synaesthesia. Nevertheless, it should be noted that other drugs, such as methadone and kava kava in controls and DXM in synaesthetes, were replicable predictors, indicating their potential as important synaesthesia predictors that are worthy of further attention. A related pattern across the analyses seems to indirectly corroborate our clustering results. Within each of our regression analyses, the models only retained two predictors from a single drug class once in controls (kava kava and gamma-Hydroxybutyric acid [GHB]) and once in synaesthetes (LSD and psilocybin) and in both cases, one of the predictors was not retained in the other regression analysis. This corroborates our foregoing supposition that different episodes of drug-induced synaesthesia seem to occur through multiple, at least partially independent, neurochemical pathways.

A subset of survey respondents reported synaesthesia under the influence of different drug classes, which suggests that some individuals may exhibit proneness to synaesthesia irrespective of the



drug being consumed. We quantified SP by weighting frequency of induced synaesthesia according to the inverse of incidence rates of induced synaesthesia for each drug, considering the total number of drugs an individual has consumed. The distributions of these scores in controls and synaesthetes suggest skewed distributions with most individuals displaying low SP with a correspondingly low incidence rate of high SP. An outstanding question is whether SP aligns with other individual differences factors previously related to synaesthesia and this will be worth exploring in future research. For example, previous research suggests that these and other anomalous percepts experienced in response to psychedelics correlate with psychological absorption, the tendency to experience all-encompassing attentional and affective engagement in a task or mental representation (Studerus et al., 2012), although the use of this scale has been criticized because of its item content (Terhune & Jamieson, 2021). Despite these interesting results, a limitation of this approach is that our indices of SP and induction are confounded by drug use: synaesthesia-prone individuals who are not drug users will necessarily score low on this measure. Nevertheless, our findings suggest that there are individuals who are more likely to experience synaesthesia in response to various recreational drugs, and that this proneness is elevated among those self-identifying as developmental synaesthetes. It also remains unclear whether, and to what extent, SP is shaped by response biases driven by participant compliance or expectancy effects. The characteristics and mechanisms of SP warrant further attention in future research in this domain.

## 4.2 | Types of drug-induced synaesthesia

Previous research on drug-induced synaesthesia using MDMA, ketamine and psilocybin (Studerus, 2013) found these primarily induce experiences of auditory-visual synaesthesias (with sounds as inducers; Griffiths et al., 2011; Studerus, 2013) and a review of this literature similarly found that auditory-visual synaesthesias were the most common (Luke & Terhune, 2013). By contrast, the subjective experience of sound-colour synaesthesia was not found to be more common than grapheme-colour synaesthesia in a controlled trial of LSD (Terhune et al., 2016). We evaluated these effects by studying the types of induced synaesthesia among the four most potent synaesthesia-inducing drug classes (tryptamines, phenethylamines, dissociatives and salvia). We again found that sound-colour synaesthesia was the most common form of drug-induced synaesthesia, followed by other sound-inducer synaesthesias such as sound-shape and sound-space synaesthesia. As in previous research (Luke & Terhune, 2013), grapheme-colour synaesthesia, among the most prevalent and most well-studied forms of this condition (Ward, 2013), was rarely encountered in this study although it has been reported in previous cases of drug-induced synaesthesia (Brang & Ramachandran, 2008; Luke, 2012). We did not observe any clear differences in the types of induced synaesthesia across different drug classes, which potentially suggests that the neurochemical mechanisms of drug-induced synaesthesia are not modality-specific. Collectively,

these data corroborate the previously observed finding that auditory stimuli seem to be the most frequent inducers in cases of spontaneous drug-induced synaesthesia (Luke & Terhune, 2013). This pattern is potentially confounded by the fact that users of recreational drugs are probably more likely to listen to music whilst consuming drugs, thereby artificially enhancing the incidence of sound-induced synaesthesia (but see Terhune et al., 2016). Accordingly, it is imperative that future research index contextual factors and concurrent activities during induced synaesthesia.

## 4.3 | Neurochemical and neurocognitive mechanisms

To date, there are two proposed neurochemical mechanisms for synaesthesia. The first, most commonly referenced hypothesis, is that synaesthesia occurs as a result of serotonin cascades (Brang & Ramachandran, 2008). Given the wealth of studies implicating 5-HT<sub>2A</sub> serotonin receptors in induced synaesthesia (Luke & Terhune, 2013), they have been proposed as the 'synaesthesia receptors' (Brang & Ramachandran, 2008). Further preliminary supporting evidence comes from studies suggesting that 5-HT<sub>2A</sub> receptor inhibition may block the experience of synaesthesia (Brang & Ramachandran, 2008; Kometer et al., 2013). Additionally, findings from human brain imaging studies with LSD indicate that reductions in default mode network integrity driving functional hyperconnectivity between the parahippocampal cortex and visual cortex (Kaelen et al., 2016) and the claustrum and auditory cortex (Barrett et al., 2020) may underpin some of the classic psychedelic sensory phenomena such as synaesthesia. Expanding upon this idea, Brogaard (2013) proposed that excessive levels of serotonin or serotonin receptor agonists activating 5-HT<sub>2A</sub> receptors in cortical neurons is a mechanism shared by (at least some cases of) congenital, acquired or drug-induced synaesthesia. According to this account, excessive serotonin release triggers selective hyperexcitability in visual cortices leading to aberrant perceptual states. This is consistent with visual cortex hyperexcitability in developmental synaesthesia (Terhune et al., 2011; Terhune, Song, et al., 2015) and in trained synaesthesia (Rothen et al., 2018; see also Lungu et al., 2020). Elsewhere, we have argued that these effects are alone unlikely to produce the hallmark behavioural features of developmental synaesthesia (e.g., automaticity and inducer-concurrent consistency). Rather, we maintain that these features arise from a consolidation process in which inducer-concurrent associations are driven by statistical regularities in one's environment (Witthoft & Winawer, 2013), resulting in the consolidation of inducer-concurrent associations over time (Simner et al., 2008). This perhaps helps to explain why induced synaesthesias do not seem to meet conventional synaesthesia criteria for automaticity and consistency (Terhune et al., 2016) whereas, at least in one case, acquired synaesthesia does (Yanakiya et al., 2019).

A second (disinhibition) hypothesis proposes instead that attenuated  $\gamma$ -aminobutyric acid (GABA) results in disruption of inhibitory activity, which in turn gives rise to synaesthesia (Hubbard

et al., 2011; Specht, 2012). According to this account, disinhibited feedback from higher cortical areas - proposed to be responsible for synaesthesia - are associated with lower GABA levels in brain regions specific to the type of synaesthesia (Hubbard et al., 2011; Specht, 2012). The aforementioned results regarding selective cortical hyperexcitability in developmental synaesthesia (Terhune et al., 2011; Terhune, Song, et al., 2015) and trained synaesthesia (Rothen et al., 2018) are consistent with this account, as are other data (Brauchli et al., 2018), although this hypothesis has received less attention than a serotonin hypothesis in the context of drug-induced synaesthesia. Moreover, the simplistic notion of lower GABA levels corresponding to cortical inhibition is not consistent with current insights into the complexity of the role of GABA in both cortical inhibition and excitation (Marafiga et al., 2021).

The present results provide novel data that has bearing on these models. As described above, our results corroborate previous research implicating serotonin in drug-induced synaesthetics and our data clearly point to the likely involvement of serotonin in induced synaesthesia. Classic psychedelics are also known to modulate dopamine (Araújo et al., 2015), although their primary subjective psychological effects are serotonergic (Libânio & Osório, 2019), and dopamine is unlikely to play a key role in inducing synaesthesia as drugs known to modulate dopamine levels (e.g., cocaine) were characterized by low incidence rates of induced synaesthesia. Nevertheless, a challenge to a simple serotonergic hypothesis is presented by *Salvia divinorum*, which exhibited the fourth highest incidence rate in our study and yet is not known to target serotonin receptors (Addy, 2011), but rather exclusively kappa opioid receptors (see also Babu et al., 2008). Moreover, to our knowledge, there is no clear evidence for aberrant serotonin receptor activity in developmental synaesthesia (e.g., Terhune, et al., 2014).

By contrast, our results do not support GABAergic disinhibition models of synaesthesia as GABA agonists (e.g., nitrous oxide, GHB, and muscimol in *Amanita muscaria*) were reliably associated with reports of induced synaesthesia in both controls and developmental synaesthetes (see also Luke & Terhune, 2013), albeit to a lesser extent than with tryptamines, phenethylamines, *Salvia*, and other dissociatives. These results are at odds with a simple GABAergic model of induced synaesthesia, according to which GABA agonists would be expected to suppress synaesthesia in developmental synaesthetes. By contrast, GABA antagonists would be expected to facilitate the induction of synaesthesia in non-synaesthetes. Disinhibition models of synaesthesia have not yet precisely specified the GABAergic mechanisms of developmental or induced synaesthesia and require further elucidation. However, our results are superficially inconsistent with this model, as is previous research using magnetic resonance spectroscopy, which demonstrated that developmental synaesthesia was not characterized by atypical GABA concentrations in primary visual cortex (Terhune, Murray, et al., 2015). Taken together, our results are broadly congruent with a serotonergic hypothesis but suggest also multiple potential neurochemical mechanisms (e.g., kappa opioid receptors) by which recreational drugs can trigger spontaneous synaesthesia.

Collectively, these different findings suggest that drug-induced synaesthesia is unlikely to be *specific* to a particular neurochemical system, although experimental research is required to assess this possibility more rigorously. If non-specificity holds, drug-induced synaesthesia is potentially consistent with models proposing that synaesthesia is a product of neural noise (Lalwani & Brang, 2019; Shriki et al., 2016). In particular, excessive neural noise (e.g., in occipital cortex) may lead to stronger synaesthesia-like states through stochastic resonance, whereby signal transmission along multisensory pathways present in all individuals is transiently enhanced (Lalwani & Brang, 2019). This model is consistent with research demonstrating that LSD produces transient basal increases in occipital cortex activity (e.g., Carhart-Harris et al., 2016; Roseman et al., 2016). Such increases would be expected to covary with the extent to which these drugs trigger transient episodes of synaesthesia-like experiences. In addition, repeated experience of these associations will promote consolidation over time and thus may help to explain cases of acquired synaesthesia following excessive drug use (e.g., Yanakieva et al., 2019). Further research on drug-induced synaesthesia should aim to more explicitly test predictions from these models (Lalwani & Brang, 2019; Shriki et al., 2016).

#### 4.4 | Limitations

A potential limitation of this study is the online recruitment of our samples and administration of the survey. This allowed us to collect data from a large, diverse sample that otherwise would have been challenging to recruit in a traditional laboratory-based study but did not permit control over the manner in which the data were collected. Insofar as our results are broadly commensurate with the extant literature it seems that online administration is unlikely to have produced systematic biases or errors. This aligns with research indicating that online surveys typically yield results similar to those conducted in laboratory contexts (Dandurand et al., 2008; Gravetter & Forzano, 2018). Our observation of non-random clustering of the incidence rates across drug classes further attests to meaningful patterns across participants, which, along with the large sample sizes, further mitigates concerns regarding reporting accuracy, and variations occurring with dosage. Relatedly, we did not collect potentially important demographic data on our sample (e.g., ethnicity) and thus the extent to which our sample is representative of the general population is unclear. Although we suspect the patterns observed here (e.g., drug class clustering) will generalize across different ethnic groups, further research is required to address this question. In particular, previous survey research found that drug use varies across different ethnic groups (Demant et al., 2018) and thus it is plausible that these groups will exhibit differential incidence rates of drug-induced synaesthesia. However, it should be noted that we did not observe an association between incidence rates for drug use and drug-induced synaesthesia.

A further limitation of this study is that we based our determination of developmental synaesthesia, as well as the lack thereof, on

self-report. This diverges from the extant synaesthesia literature, in which identification of this condition typically includes measures of inducer-concurrent automaticity and/or consistency (Eagleman et al., 2007; Rothen et al., 2013; Ward, 2013). These procedures were not incorporated into our study as they were not yet available for online implementation when this study was conducted. Self-reported assessment of synaesthesia has been used in the past for validating these measures (Eagleman et al., 2007) but may have inflated the incidence of false positive reports of synaesthesia (Carmichael et al., 2015) and developmental synaesthetes incorrectly self-reporting as controls. However, synaesthetes were recruited from established channels where individuals are unlikely to be confused regarding their status as a synaesthete (as opposed to an unselected sample). In addition, our finding that the incidence of self-reported familial synaesthetes (2%) falls within the prevalence range of this condition (1%–4%; Ward & Simner, 2020), suggests that the false negative rate is unlikely to be high. A related point is that the drug use incidence rates should not be taken as representative of the rates in the general population because of the method of participant recruitment. In particular, participants were explicitly recruited for a study on drug use in order to ensure that we were able to capture use of a wide variety of drugs with a limited sample size. In turn, it is likely that our method of recruitment would be more likely to attract active drug users, rather than a completely representative sample, and this is likely reflected in the high incidence rates of specific drugs. These limitations warrant the use of caution in interpreting the present results, but are unlikely to have confounded the incidence rates of drug-induced synaesthesia (see the near-zero correlation between these two incidence rates) and the clustering of rates by drug class, which were similar in controls and synaesthetes.

#### 4.5 | Future directions

The present study expands upon previous research on drug-induced synaesthesia by studying a wider array of drugs than previous studies. Our results corroborate multiple findings in the extant literature but also raise new questions that warrant further attention. Future controlled pharmacological research on drug-induced synaesthesia should directly contrast drugs that act on 5-HT<sub>2A</sub> serotonin receptors against those that modulate other neurochemicals. In particular, it will be imperative to formally test predictions derived from serotonergic and GABAergic models of synaesthesia (e.g., Terhune et al., 2014). It will also be necessary to compare the neurophysiological characteristics of such effects against those observed with developmental synaesthesia. Such experiments are also required to more clearly elucidate whether the frequent observation of sounds as inducers of spontaneous synaesthesia (Luke & Terhune, 2013) represents a genuine feature of induced synaesthesia or a contextual artefact. Our results suggest that a small subset of individuals may be especially prone to induced synaesthesia across different drug classes. Further study of these individuals has the potential to significantly advance our understanding of the conditions under which

induced synaesthesia occurs. There has been almost no research on the impact of recreational drugs on developmental synaesthesia but we believe further research on this topic similarly has the potential to inform our understanding of the neurochemical pathways underlying this condition.

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#### CONFLICT OF INTEREST

The authors report no conflicts of interest. All authors have approved the final manuscript. This is original unpublished work and is not being submitted for publication elsewhere.

#### AUTHOR CONTRIBUTIONS

David P. Luke and Devin B. Terhune devised the study and developed the materials, Ross Friday oversaw the data collection, David P. Luke, Laura Lungu, and Devin B. Terhune conducted the statistical analyses, and David P. Luke, Laura Lungu, Ross Friday, and Devin B. Terhune contributed to the preparation of the manuscript and approved the final draft.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in OSF at <https://osf.io/x45yf/>.

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