

Acquired synaesthesia following 2C-B use^a

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Contributors

SY: study concept and design, data acquisition, analysis and interpretation of data, drafting/revising the manuscript. DPL: study concept and design, data interpretation, revising the manuscript. AJ: study concept and design, data interpretation, revising the manuscript. DBT: study concept and design, data acquisition, analysis and interpretation of data, drafting/revising the manuscript.

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Psychedelic drugs reliably trigger experiences that closely resemble *synaesthesia* (Luke and Terhune 2013), a condition in which inducer stimuli will reliably and automatically elicit atypical concurrent experiences (Ward 2013). These transient episodes are considered controversial because they do not meet behavioural diagnostic criteria for developmental synaesthesia (Terhune et al. 2016). However, if these behavioural markers are attributable to the consolidation of synaesthetic associations over time (Terhune et al. 2016), they should be observed in cases of acquired synaesthesia. Here we report a case of drug-induced acquired synaesthesia (LW) that meets standard diagnostic criteria for developmental synaesthesia.

LW is a 29-year-old male who reports continuously experiencing multiple forms of synaesthesia for over 7 years since ingesting approximately 70-150mg of 2,5-dimethoxy-4-bromophenethylamine (2C-B) (Papaseit et al. 2018), which greatly exceeds the normal dosage (12-24mg) (Shulgin and Shulgin 1990) (see **Supplementary Materials**). LW was contrasted against 10 non-synaesthete healthy controls, all of whom provided informed written consent. He reports that his synaesthetic associations became more stable over time and his response patterns met inducer-concurrent consistency thresholds for week-color and instrument-color, but not chord-color, synaesthesia on a standardized battery (Eagleman et al. 2007). He experiences colours as visuospatially co-localized with inducing faces (projector synaesthesia (Dixon et al. 2004; Terhune et al. 2015)), which was corroborated (Skelton et al. 2009). He reports that none of his immediate family members have developmental synaesthesia; two individuals who have known him since before the onset of his synaesthesia independently corroborated his reports. The transient induction of synaesthesia-like experiences through 2C-B use has been widely reported in online discussion forums of recreational drug users as well as in a previous survey of drug users (Luke et al. 2012) but we are unaware of any reports of acquired synaesthesia through the use of 2C-B or any other drugs.

To assess the automaticity of LW's face-colour synaesthesia, one of the hallmark behavioural features of developmental synaesthesia (Ward 2013), he was contrasted against controls on a priming task in which face primes were presented prior to judgments of color patches that were either congruent or incongruent with the preceding prime according to LW's face-color associations. LW displayed a larger congruency effect (incongruent – congruent) in error rates, 80% [95% CIs: 71, 88],

than controls, 2% [0.2, 2.6], $t(9)=37.13$, $p<.001$ (**Figure 1**), reflecting a difference of nearly 39 *SDs*, $z_{cc}=38.95$ [38.40, 39.56], with a very low probability of occurrence in the general population, $p_{gp}=1.8^{-9}\%$ [1.6⁻⁹, 2.1⁻⁹]. LW's congruency effect in response times for correct responses was also larger, 236ms [24, 507], than that of controls, 20ms [-1, 48], $t(9)=5.07$, $p<.001$, corresponding to a difference of over 5 *SDs*, $z_{cc}=5.32$ [4.63, 5.83], and a very low probability of occurrence, $p_{gp}=3^{-2}\%$ [2⁻², 8⁻²]. Bootstrap resampling revealed that LW's response distributions in congruent and incongruent conditions were completely independent for error rates and only minimally overlapping for response times whereas both sets of distributions overlapped considerably in controls.

LW's multiple forms of synesthesia exhibited inducer-concurrent consistency and his face-color synesthesia exhibited automaticity, thereby meeting the two most widely used behavioural diagnostic criteria for synesthesia (Eagleman et al. 2007; Rothen et al. 2013; Ward 2013). Insofar as these criteria are not met by transient episodes of drug-induced synaesthesia, these results are consistent with the proposal that automaticity and consistency are byproducts of the over-learning of associations rather than behavioural signatures of synaesthesia *per se* (Terhune et al. 2016).

Insofar as 2C-B is a partial serotonin agonist (Páleníček et al. 2013; Papaseit et al. 2018), these results add to a growing body of evidence implicating serotonin in the development of synaesthesia (Brogaard and Gatzia 2016; Luke and Terhune 2013). Although LW did not experience synaesthesia prior to consuming 2C-B, we cannot rule out the possibility that 2C-B use interacted with a latent predisposition for cortical disinhibition or hyperexcitability (Rothen and Meier 2014; Terhune et al. 2015). The factors that sustained his synaesthesia are unknown but its continuity is plausibly attributable to the excessive dose of 2C-B (Shulgin and Shulgin 1990). Excessive serotonin from LW's 2C-B use (Papaseit et al. 2018) may have triggered elevated glutamate release, and concomitant hyperexcitability in visual cortex (Brogaard and Gatzia 2016), a neurophysiological characteristic of synaesthesia (Terhune et al. 2015; Terhune et al. 2011). Cortical hyperexcitability may have triggered sustained visual colour percepts that were perceived as visuospatially co-localized with environmental inducers similar to the induction of hallucinogen persisting perception disorder (HPPD), which may also have a serotonergic basis (Litjens et al. 2014; Martinotti et al. 2018).

Figure 1. Face-color automaticity in an acquired synaesthete (LW) and controls. Markers reflect 1,000 bootstrap resamples for LW and control means in congruent and incongruent face-color priming conditions. Marginal histograms reflect kernel density plots of the bootstrap distributions.

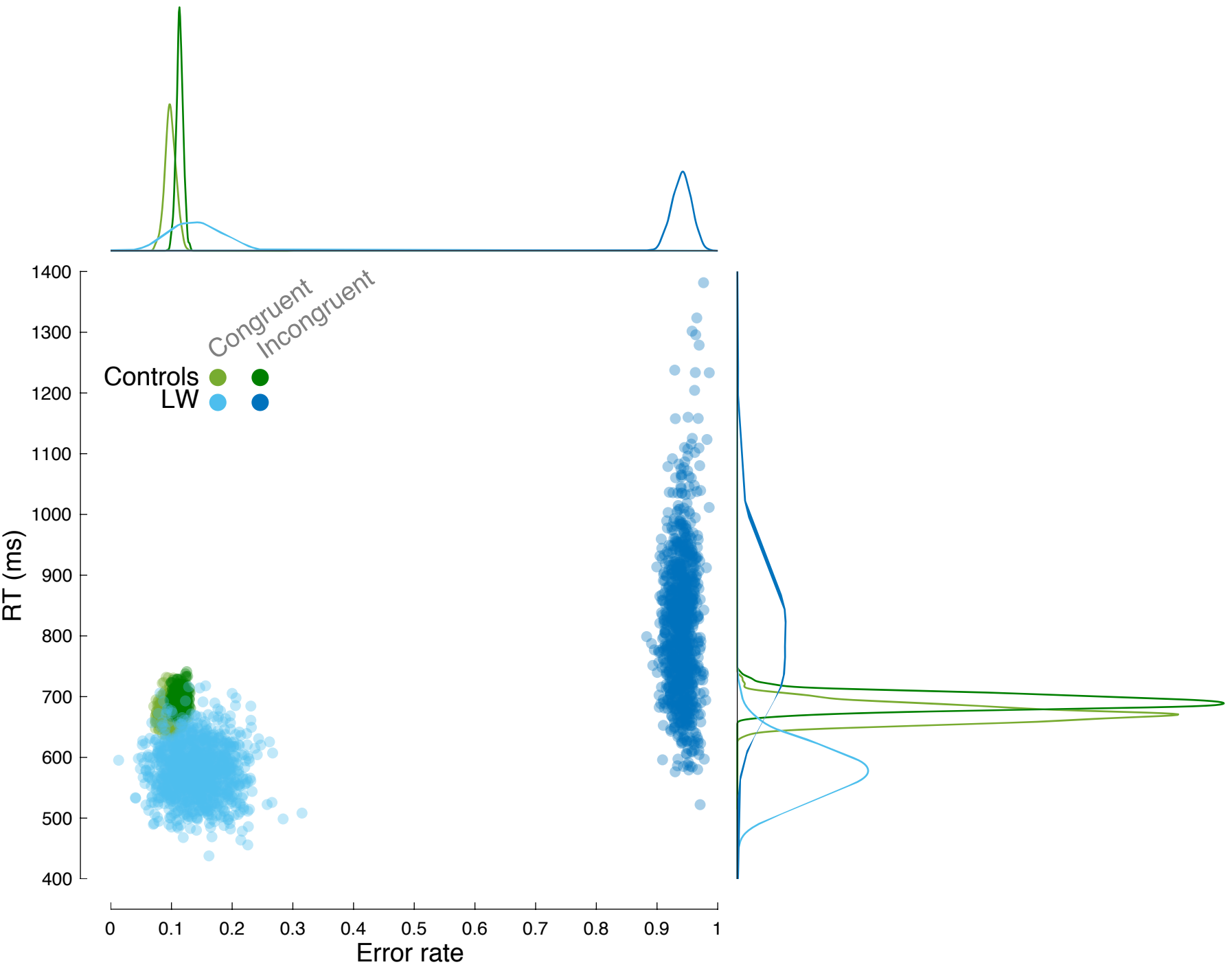
Compliance with ethical standards

The authors report no conflicts of interests.

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SUPPLEMENTARY MATERIALS

Acquired synaesthesia following 2C-B use

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Methods

Participants

LW is a 29-year-old left-handed male and native English speaker with 3 years of higher education. He reports continuously experiencing multiple forms of synaesthesia for over 7 years since ingesting approximately 70-150mg of 2C-B (approximately 3-12 times the normal dosage [12-24mg]) (Shulgin and Shulgin 1990) at the age of 22. Ten healthy male participants, who were recruited for a study on perception, without reference to synaesthesia, color processing, or drug use, served as controls (see **Table S1**). Controls ranged in age between 20 and 54, $M=28.9$ [95% CIs: 25.3, 38.0], with years of higher education ranging from 0 to 6 ($M=3.7$; $SD=1.6$). Seven of the controls were native English speakers, four were left-handed, five were right-handed, and one was ambidextrous. None of the controls reported having developmental synaesthesia. LW and the controls did not differ in age, $t(9)=0.01$, $p=.50$, $z_{cc}=0.01$ [-0.96, 0.40], $p_{gp}=50\%$ [36, 81], or years of education, $t(9)=0.41$, $p=.65$, $z_{cc}=0.43$ [-0.92, 0.31], $p_{gp}=65\%$ [39, 80]. All participants were compensated for taking part in the study and provided informed consent in accordance with local ethical approval.

Materials

Drug use history. To screen for drug use history, participants completed the *Psychoactive Drug History Questionnaire* (PDHQ) (Sobell et al. 1995). This scale indexes drug use in the following

categories: alcohol, cannabis, stimulants, amphetamines and other stimulants, benzodiazepines and tranquilizers, sedatives, hypnotics and barbiturates, heroin, street of illicit methadone, other opioids, hallucinogens (LSD, PCP, STP, MDA, DAT, mescaline, peyote, mushrooms, ecstasy (MDMA), nitrous oxide (NO)), inhalants, and others. The following drugs were added to the existing (hallucinogens) category: 2C-B, DMT, ayahuasca, salvia, DXM, 2-CT, ketamine, datura, *Amanita muscaria*, GHB, ether, and kava kava, as these have all been previously associated with reports of drug-induced synaesthesia (Luke and Terhune 2013; Luke et al. 2012).

Table S1. Demographic information and drug use history in LW (acquired synaesthete) and controls (Ctrl).

	LW	Ctrl	Ctrl	Ctrl	Ctrl	Ctrl	Ctrl	Ctrl	Ctrl	Ctrl	Ctrl
Age (years)	29	25	31	26	22	30	54	29	25	20	27
YoE (years)	3	3	5	4	4	3	4	6	3	0	5
Handedness	L	R	R	R	L	L	R	R	L	L/R	L
Face Memory (UFMT)	86	95	77	82	89	85	89	63	82	86	96
Face-colour priming RT (ms)											
Congruent	576	552	685	581	514	803	754	800	871	667	498
Incongruent	812	601	663	683	571	802	747	821	900	636	499
<i>Error rate</i>											
Congruent	.139	.013	.055	.575	.014	.055	.041	.041	.055	.055	.082
Incongruent	.940	.023	.051	.618	.028	.032	.051	.074	.060	.092	.111
Alcohol	+	+	+	+	+	+	+	+	+	+	+
Cannabis	+	+	+	-	+	+	+	+	+	+	+
Stimulants & amphetamines	+	+	+	-	-	+	-	-	+	-	-
Benzodiazepines	+	-	+	-	+	-	-	-	+	-	-
Opioids	-	-	+	-	-	-	-	+	+	-	-
Hallucinogens	Peyote, psilocybin, MDMA, NO, 2C-B*, ketamine, Changa, cannabis	MDMA	LSD*, MDA, mescaline*, psilocybin*, MDMA, NO, 2C-B, DMT, psilohuasca	-	-	LSD*, psilocybin*, MDMA, NO, 2C-B, salvia, ketamine, cannabis*	-	-	LSD*, psilocybin, MDMA*, NO, Datura	-	-
Hallucinogen use in the previous 6 months	Peyote (1) Psilocybin(1)		LSD (4) MDA (2) Psilocybin (9) MDMA (4)	-	-	Psilocybin (1) MDMA (1)	-	-	LSD (1) MDMA (6)	-	-

Note. YoE= completed years of university education; L/R= ambidextrous; += previous use; -= no previous use; 2C-B = 2,5-dimethoxy-4-bromophenethylamine; MDMA= 3,4-Methylenedioxyamphetamine; LSD=Lysergic acid diethylamide; NO = Nitrous Oxide; DMT = N-Dimethyltryptamine; MDA= 3,4-Methylenedioxyamphetamine. * Participant reported synaesthesia under the influence of this drug. Numbers denote frequency of use in the previous 6 months.

Synaesthesia screening. All participants completed a questionnaire that provided a definition of synaesthesia and specific examples (Terhune et al. 2016). They were presented with descriptions of canonical forms of synaesthesia (grapheme-color, sound-color, and spatial sequence) and asked if they had these or any other forms of synaesthesia. In addition, they were questioned regarding the

experience of synaesthesia under the influence of drugs, which drugs, frequency (“rarely”, “some of the time”, “most of the time”, “every time”), and the type(s) of drug-induced synaesthesia. All participants completed the synaesthesia battery (Eagleman et al. 2007), a widely-used online instrument for assessing inducer-concurrent consistency in different forms of synaesthesia. LW also completed the visually-illustrated associator-projector scale (Skelton et al. 2009), which indexes the extent to which a synaesthete experiences their phosphenes as images (associator) or visuospatially co-localized with the inducer (projector) (Dixon et al. 2004).

Face memory. To assess the extent to which LW may exhibit atypical face processing or face memory, participants completed the *Unfamiliar Face Memory Test* (UFMT; Jansari, *in preparation*). The UFMT is modelled on the long form of the *Cambridge Face Memory Test* (CFMT; (Russell et al. 2009)). The task involves learning and recognizing black and white images of male faces generated with FaceGen (<https://facegen.com>). The faces are presented under different learning conditions followed by a series of 3-alternative forced choice recognition tests. The task is comprised of five different sections with the learning and memory conditions becoming increasingly more difficult. Mean accuracy is 83 ($SD=11$) and the UFMT is able to capture a range of abilities from so-called super-recognition to prosopagnosia. UFMT performance correlated highly with CFMT performance in a normative sample, $r(59)=.83$, $p<.001$ (Jansari, *in preparation*), thereby demonstrating construct validity.

Face-color priming. This task examined whether affective faces associated with specific colors by LW would elicit automatic color experiences that would *facilitate* or *interfere* with subsequent color judgments, as observed in developmental synaesthesia (Gebuis et al. 2009; Terhune et al. 2011). Each trial consisted of a blank screen (300ms), a face prime (5.5 x 3.8cm; 1000ms), a blank inter-stimulus interval (500ms), and a color patch (5.5 x 3.8cm; 500ms). Participants were instructed to focus on the center of the monitor at all times and identify the color of the patch as quickly and as accurately as possible by depressing one of four response keys using the index and middle fingers of their left and right hands using a keyboard. Face stimuli consisted of four affective faces (*anger, disgust, happiness,*

and *surprise*) drawn from a validated database (Langner et al. 2010). The faces consisted of 2 white females, 1 black male, and 1 white male and the color patches included the colors blue, orange, green, and purple. Face-colour pairings (according to LW's associations) were congruent on 25% of trials.

Procedure

To ensure consistency, LW and all controls completed the tasks in the same order. In all cases, task instructions were presented on the computer monitor and verbally administered by the experimenter. After completing the different psychometric measures, participants completed the face-color priming task. Participants were positioned approximately 70cm from the screen. Stimulus presentation was implemented using PsychoPy2 v1.85.3 (Peirce et al. 2019), on a 21inch desktop computer. In the face-colour priming task, participants completed one practice block of 16 trials, followed by three experimental blocks of 96 randomized trials, amounting to 288 trials. Participants completed 114 trials in the UFMT.

Data analysis

All comparisons of LW and controls were conducted with modified independent t -tests (Crawford and Howell 1998) and effect size estimates (z_{cc}) (Crawford et al. 2010) for single-case studies. The percentage of the general population (p_{gp}) that displays a more extreme value was estimated from p -values (Crawford and Garthwaite 2002). Bootstrap resampling (10,000 resamples, bias-corrected and accelerated method) (Efron 1987) was used to compute 95% confidence intervals (CIs) for different point estimates. Response patterns in the face-color priming task were investigated by analyzing error rates and mean response times on correct trials (RTs). Raw data are presented in Table S1. **Figure 1** was created by resampling data (1,000 samples) and iteratively computing the dependent measure in each condition.

Results

Case

LW reports not experiencing synaesthesia during childhood and adolescence including under the influence of recreational drugs. In July 2010 at the age of 22, LW first used 2C-B (approximately 10-15mg) but did not experience synaesthesia. He subsequently ingested a high dose (70-150mg) of 2C-B in September 2010, which greatly exceeds the normal oral dosage (12-24mg) (Shulgin and Shulgin 1990), and experienced multiple vivid forms of synaesthesia including day-color, sound-color, emotion-color, smell-color, and face-color synaesthesia. He reports that he continued to experience these different forms of synaesthesia afterward and continues to report these experiences 7 years after this episode (this study was conducted in September 2017). LW reports that his strongest form of this condition is face-color synaesthesia, in which faces will involuntarily elicit experiences of color and he reports that these effects are enhanced by emotional facial expressions. He experiences colours as visuospatially co-localized with inducing faces (projector synaesthesia; (Dixon et al. 2004; Skelton et al. 2009; Terhune et al. 2015a; Ward 2013)). LW's reports closely resemble reported cases of developmental face-color synaesthesia (Farina et al. 2017; Terhune et al. 2010; Ward 2013) and his associations between color and emotion are consistent with emotion-color links in the general population (Dael et al. 2016). He reports that his synaesthesia is attenuated after consumption of coffee, alcohol, cigarettes, and cannabis, and enhanced after consumption of ketamine, psilocybin, and 2C-B, as previously reported in developmental synaesthesia (Luke and Terhune 2013). LW reports that none of his immediate family members have developmental synaesthesia. Two individuals who knew LW prior to, and after, the onset of his synaesthesia were interviewed and confirmed that he did not report such experiences prior to his 2C-B use, that he first reported these experiences shortly after consuming 2C-B in September 2010, and that he has continuously reported synaesthetic experiences since that date.

Synaesthesia characteristics

LW was assessed for inducer-concurrent consistency for three forms of synaesthesia (week-color, instrument-color, and chord-color) using the synaesthesia battery (Eagleman et al. 2007). For these

three forms, he received scores of 1, 0.49, and 2.01, respectively. Scores of 1 and below have been shown to reflect synaesthesia (Eagleman et al. 2007), although this threshold may be too conservative (Rothen et al. 2013). These results thereby suggest that LW's week-color and instrument-color synaesthesia meet criteria for consistency as applied in developmental synaesthesia. The use of face-colour associations in the face-colour priming task further necessitated the consistency of these associations as inducer-concurrent automaticity cannot be assessed in the absence of inducer-concurrent consistency, as previously noted in the study of transient drug-induced synaesthesia-like experiences (Terhune et al. 2016). In particular, although not formally tested, LW was able to identify four face-colour pairs that were stable over a one-week period, and which were used as stimuli in the face-colour priming task (see below). LW completed the associator-projector questionnaire (Skelton et al. 2009) in reference to his face-color synaesthesia and received a score of 7, which meets criteria for projector synaesthesia (>4.3) and is thereby consistent with his reports that synaesthetic colour are perceived as visuospatially co-localized with inducers.

Face memory

A wealth of evidence suggests that synaesthetes display superior memory on a range of tasks (Rothen et al. 2012). In order to determine whether LW displayed atypical face processing or memory, we compared his performance on the UFMT against that of controls. LW responded correctly on 86 (out of 114) trials, which was comparable to the controls' performance, $M=84.4$ [77.4, 88.9], $t(9)=0.16$, $p=.44$, $z_{cc}=0.17$ [-0.30, 0.92], $p_{gp}=44\%$ [20, 61] (**Table S1**). All participants scored within 2 *SDs* of the mean performance in a previous normative sample ($M=83$, $SD=11$; Jansari, *in preparation*). These data suggest that LW has normal face memory.

Drug use

LW and controls exhibited similar patterns of past drug use overall although LW tended to report a greater history of drug use than most controls with only 3 controls having a comparable history, 2 of whom had histories that exceeded LW's history (**Table S1**). 4 controls (40%) reported previous experience of drug-induced synaesthesia, in all cases with psychedelic drugs, cannabis, or MDMA, as

previously reported (Luke and Terhune 2013; Luke et al. 2012). LW and 3 controls reported having used hallucinogens in the 6 months preceding the study. Cumulatively, these reports corroborate the occurrence of drug-induced synaesthesia in the general population (Luke and Terhune 2013; Luke et al. 2012) and suggest that LW's drug use history is in the upper range of males in his age range but is not atypical.

Face-colour automaticity

LW's consistent face-colour associations were used to present congruent and incongruent face primes prior to colour judgments. In addition to the effects reported in the main text (**Figure 1 and Table S1**), LW exhibited numerically faster response times on congruent trials, 576ms [498, 667], than controls, 672ms [597, 751], suggesting a moderate facilitation effect of congruent primes, $z_{cc}=0.73$ [0.13, 1.31], but this effect did not achieve statistical significance, $t(9)=0.69$, $p=.75$, $p_{gp}=75\%$ [55, 88].

Discussion

The present case speaks to a long-standing debate regarding whether drug-induced synaesthesia-like experiences qualify as genuine synaesthesia (Brogaard and Gatzia 2016; Luke and Terhune 2013; Sinke et al. 2012; Terhune et al. 2016). LW's multiple forms of synesthesia exhibited inducer-concurrent consistency and his face-color synesthesia exhibited automaticity, thereby meeting the two most widely used behavioural diagnostic criteria for this condition (Eagleman et al. 2007; Rothen et al. 2013; Ward 2013). In addition, the specific variant of his most prominent form of synaesthesia closely approximates previous cases of developmental face-colour synaesthesia (Terhune et al. 2010). These results cumulatively suggest that LW's experiences qualify as genuine synaesthesia. His synaesthesia appears to have arisen following a single dose of the recreational psychedelic drug 2C-B, a partial serotonin agonist (Páleníček et al. 2013; Papaseit et al. 2018), and thereby points to the acquisition of synaesthesia through the use of psychedelic drugs and thereby implicates serotonin in the development of synaesthesia (Brogaard 2013; Brogaard and Gatzia 2016; Luke and Terhune 2013; Terhune et al. 2016).

The present results expand upon previous research implicating psychedelic drugs in the induction of spontaneous synaesthesia-like experiences (Brogaard and Gatzia 2016; Luke and Terhune 2013). Despite reliable evidence for the induction of such episodes, a recent laboratory study found that LSD-induced synaesthesia did not exhibit inducer-concurrent consistency (Terhune et al. 2016). By contrast, LW's synaesthesia met standard diagnostic behavioural criteria for both consistency and automaticity (Rothen et al. 2013; Ward 2013). This result is consistent with the hypothesis that these two markers are actually the by-product of over-learning of synaesthetic associations rather than signatures of synaesthesia *per se* (Terhune et al. 2017; Terhune et al. 2016) (see also (Rothen et al. 2018; Simner et al. 2009). A corollary of this consolidation hypothesis is that these criteria are not useful for evaluating transient episodes of synaesthesia, only those that have undergone consolidation. To our knowledge, no previous cases of acquired synaesthesia have been evaluated against these diagnostic criteria (Afra et al. 2009; Alstadhaug and Benjaminsen 2010; Fornazzari et al. 2012; Goller et al. 2013; Roberts and Shenker 2016; Schweizer et al. 2013). We expect that cases of acquired synaesthesia will not meet diagnostic behavioural criteria at early stages, as observed in our previous study of drug-induced synaesthesia (Terhune et al. 2016), but that continued experience of synaesthesia will drive consolidation of inducer-concurrent associations, as found in developmental synaesthesia (Simner et al. 2009), eventually leading to automaticity and consistency, as shown in training studies with non-synaesthetes (Rothen et al. 2018).

A striking feature of the present case that contrasts with those previously reported in the literature (Luke and Terhune 2013) is that LW's synaesthesia persisted for over seven years. The transition from a transient episode to a continuous acquired condition is plausibly attributable to the excessive dose of 2C-B, which greatly exceeded the normal recreational dose of this drug (Shulgin and Shulgin 1990). Excessive serotonin from LW's 2C-B overdose (Papaseit et al. 2018) may have triggered elevated glutamate release and concomitant hyperexcitability in visual cortex (Brogaard 2013; Brogaard and Gatzia 2016), a neurophysiological characteristic of developmental synaesthesia (Terhune et al. 2015a; Terhune et al. 2011). Cortical hyperexcitability may have resulted in sustained visual colour percepts that were perceived as visuospatially co-localized with environmental inducers in a similar manner to the induction of hallucinogen persisting perception disorder (HPPD) (Litjens et

al. 2014; Martinotti et al. 2018). HPPD is characterized by the sustained or recurrent experience of (primarily visual) perceptual distortions in the absence of recent drug use and may also have a serotonergic basis (Litjens et al. 2014; Martinotti et al. 2018). LW's face-colour synaesthesia is phenomenologically similar to reports of coloured halos around objects in HPPD and synaesthesia is among the set of visual disturbances reported in this disorder. The induction of synaesthesia might have been facilitated by increased functional connectivity in multisensory pathways as preliminary non-human animal research suggests that at high doses (50mg/kg), 2C-B enhances functional connectivity in upper beta (25-30Hz) and lower gamma (30-40Hz) bands (Páleníček et al. 2013), both of which have been implicated in developmental synaesthesia (Brauchli et al. 2018; Terhune et al. 2015b). Impaired lateral geniculate nucleus functioning in the thalamus has been suggested to play a role in HPPD (Martinotti et al. 2018), which also potentially aligns with cases of acquired synaesthesia after thalamic stroke (Fornazzari et al. 2012; Schweizer et al. 2013). Despite these parallels, it remains an open question under what circumstances HPPD may give rise to acquired synaesthesia. By contrast, insofar as a single dose of 2C-B is unlikely to produce radical and focal changes in brain structure connectivity (Brogaard and Gatzia 2016), these results challenge the view that structural hyperconnectivity is a causal antecedent to synaesthesia (Hubbard et al. 2011). Rather, they suggest instead that, structural brain differences in synaesthesia are a consequence of the consolidation of synaesthetic associations (Cohen Kadosh and Walsh 2008; Terhune et al. 2016).

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