ORIGINAL INVESTIGATION

LSD enhances suggestibility in healthy volunteers

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Abstract

Rationale Lysergic acid diethylamide (LSD) has a history of
use as a psychotherapeutic aid in the treatment of mood
disorders and addiction, and it was also explored as an en-
hancer of mind control.
Objectives The present study sought to test the effect of LSD
on suggestibility in a modern research study.
Methods Ten healthy volunteers were administered with in-
travenous (i.v.) LSD (40–80 μg) in a within-subject placebo-
controlled design. Suggestibility and cued mental imagery
were assessed using the Creative Imagination Scale (CIS)
and a mental imagery test (MIT). CIS and MIT items were
split into two versions (A and B), balanced for 'efficacy' (i.e.
A≈B) and counterbalanced across conditions (i.e. 50 % com-
pleted version 'A' under LSD). The MIT and CIS were issued
110 and 140 min, respectively, post-infusion, corresponding
with the peak drug effects.
Results Volunteers gave significantly higher ratings for the
CIS ($p=0.018$), but not the MIT ($p=0.11$), after LSD than
placebo. The magnitude of suggestibility enhancement under
LSD was positively correlated with trait conscientiousness
measured at baseline ($p=0.0005$).

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Conclusions These results imply that the influence of sugges-
tion is enhanced by LSD. Enhanced suggestibility under LSD
may have implications for its use as an adjunct to psychother-
apy, where suggestibility plays a major role. That cued imag-
ery was unaffected by LSD implies that suggestions must be
of a sufficient duration and level of detail to be enhanced by
the drug. The results also imply that individuals with high trait
conscientiousness are especially sensitive to the
suggestibility-enhancing effects of LSD.

Introduction

Lysergic acid diethylamide (LSD) is an ergotamine derivative
with a high affinity for and agonist properties at several
different neurotransmitter receptors; however, signalling at
the serotonin 2A receptor (5-HT$_{2A}$R) is thought to be crucial
for its psychedelic effects (Nichols 2004). The remarkable
psychological properties of LSD were first discovered by
Albert Hofmann in 1943 (Hofmann 1980), and thereafter,
LSD was investigated as a psychotomimetic (Fabing 1955)
and tool to assist psychotherapy (Savage 1957) before regu-
latory restrictions in the mid-1960s that effectively suspended
all of the relevant scientific research (Nutt et al. 2013; Stevens
1987). In the early 1950s, cold war pressure motivated a
search for new methods to enhance interrogation and behav-
ioural control, and in this climate, a covert programme of
research code named 'MK-ULTRA' was commissioned by
the US government to explore the potential of LSD to facili-
tate mind/behavioural control (Marks 1979).

Suggestibility refers to an individual's susceptibility or
responsiveness to suggestion. Suggestions can be given for
alterations in the contents of consciousness and can target

perception, sensation, cognition, emotion or behaviour. Suggestibility can be measured behaviourally, i.e. by the performance of suggested behaviours, or subjectively via the reported vividness or realism of suggested subjective experiences. Classically, a strong response to a suggestion is accompanied by the feeling of 'involuntariness' (Weitzenhoffer 1980), and suggestions have been demonstrated which allow participants to overcome normally automatic responses, such as word comprehension in the Stroop effect (Raz et al. 2002).

Different forms of suggestibility have been proposed, e.g. primary, secondary and interrogative suggestibility (Eysenck and Furneaux 1945; Gudjonsson 2003). The present study focuses on primary suggestibility defined as the induction of thoughts and actions via suggestion (Eysenck and Furneaux 1945). Assessments of suggestibility are often delivered following a hypnotic induction and are said to assess 'hypnotizability', but the same items can be delivered in the absence of hypnosis in which case they assess 'imaginative suggestibility' (Braffman and Kirsch 1999; Hull 1933) which is the ability of an individual to engage in fantasies that have the potential to alter his/her behaviour and/or subjective experience. Hypnotic suggestibility is strongly predicted by imaginative suggestibility (Braffman and Kirsch 1999), and both can be considered forms of primary suggestibility.

Some of the most popular suggestibility scales in use in the twentieth century (e.g. the Stanford Hypnotic Suggestibility Scales) were designed to follow an initial hypnotic trance induction procedure (Barber 1995; Weitzenhoffer and Hilgard 1959), but scales of this era have been criticised for being too aggressive and authoritative in style, e.g. asserting that the participant's jaw is locked shut so that they cannot speak (Wilson and Barber 1978).

The creative imagination scale (CIS; Wilson and Barber 1978) is a suggestibility scale that was specifically designed not to require an initial trance induction nor to involve an authoritarian suggestion style, which may have risked provoking anxiety in participants under LSD (Johnson et al. 2008). The CIS involves asking participants to imagine scenarios such that their outstretched arm is becoming heavier, that they are drinking cool and refreshing water, that time is becoming distorted or that they are experiencing localised anaesthesia in their hand. It assesses the subjective intensity of these suggested effects and, therefore, measures imaginative suggestibility (Braffman and Kirsch 1999).

Suggestibility has been found to play an important role in treatment outcomes for some conditions. For example, hypnotic suggestion is an effective treatment for acute and chronic pain, and there exists an association between the suggestibility and magnitude of clinical effect (Patterson and Jensen 2003). Suggestibility may also play a role in psychotherapy outcomes (Kirsch and Low 2013; Paddock and Terranova 2001).

After a hiatus of several decades, clinical research on LSD has recently restarted, with the publication of a report documenting the safety and efficacy of LSD as an aid to psychotherapy in the treatment of anxiety related to terminal illness (Gasser et al 2014). There is presently much interest in the potential of LSD and related psychedelics to treat anxiety and mood disorders as well as addiction (Grob et al. 2011; Krebs and Johansen 2012), and relevant trials are currently underway.

The potential of LSD to enhance suggestibility was first noted by clinicians working with the drug in the 1950s. For example, the psychiatrist Mortimer Hartman commented that "the patient under LSD, from a therapeutic point of view, is quite definitely hypersuggestible" (Josiah Macy and Abramson 1960). There are two published reports from the 1960s on the suggestibility-enhancing effects of LSD. The first employed a measure of imaginative suggestibility (i.e. the 17-item Stanford Suggestibility Scale) delivered without a hypnotic induction (Weitzenhoffer and Hilgard 1959) in a within-subject design involving 24 healthy participants and compared the effects on suggestibility of LSD (1.5 μg/kg), psilocybin (225 μg/kg), mescaline (5 mg/kg), all 3 drugs combined and hypnosis in the absence of drugs (Sjoberg and Hollister 1965). Two different versions of this scale were administered before and 2–3 h after ingestion of each drug and separately before and after hypnotic trance induction. Results showed that suggestibility was significantly enhanced by LSD, mescaline, the three drugs in combination and hypnosis, but not by psilocybin alone. The second study looked at the effect of LSD (75 μg i.v.) on a single body sway suggestion (i.e. a forward and back swaying made in response to suggestion) in 11 'neurotic' patients, 15 patients with depression and 10 with schizophrenia in a within-subject placebo (i.v. saline) controlled design (Middlefell 1967). Suggestion began 90 min post-infusion, and test days were separated by 48 h and conducted in a balanced order. LSD significantly enhanced body sway relative to placebo, and this effect was most pronounced in the neurotic patients and least so in the depressives.

The present study sought to test the hypothesised suggestibility-enhancing effects of LSD in a modern placebo-controlled study. Consistent with a previous study investigating the effects of nitrous oxide on suggestibility (Whalley and Brooks 2009), it also sought to address the effect of the drug on cued mental imagery using a modified version of the Questionnaire upon Mental Imagery (QMI; Sheehan 1967). This task involves instructing the participant to imagine, with eyes closed, a succession of sensory experiences such as the taste of honey or the smell of freshly cut grass (see 'Methods' for details). Baseline measures of depressive symptoms and personality traits were acquired ahead of testing days to assess their potential predictive value in relation to the primary experimental outcomes. The primary hypotheses were that both suggestibility and cued mental imagery would be significantly enhanced by LSD.

Methods

Experimental design

This study received a favourable opinion from NRES committee London, West London, and was conducted in accordance with the revised Declaration of Helsinki (2000), the International Committee on Harmonisation Good Clinical Practice guidelines and NHS Research Governance Framework. Imperial College London sponsored the research, and a Home Office license was obtained for research with schedule one drug.

LSD was administered via intravenous infusion (40–80 μg in 10 ml saline) over 3 min in a single-blind, within-subject, placebo-controlled design. Experimental sessions were conducted in the Wellcome Trust Clinical Research Facility (WTCRF) at the Hammersmith Hospital site, London. Placebo (10 ml saline) was administered 5–10 days prior to LSD, thus avoiding potential carry-over effects from LSD into the placebo condition. Since a primary motivation of this study was to determine a safe and appropriate dose of LSD for a subsequent neuroimaging study, the dosage of LSD varied among subjects, i.e. one received 40 μg, two 50 μg, six 70 μg and one 80 μg. Thus, a total of 10 subjects received LSD in this study. The relevant tasks, i.e. a mental imagery test (MIT) and the CIS, were issued 110 and 140 min post-infusion, respectively, corresponding with the peak intensity of the drug's subjective effects. Participants were recruited via word-of-mouth, making this a 'convenience' or 'opportunity' sample. Lastly, it is worth noting that the comparative dose effects of intravenously and orally administered LSD are much more similar than, e.g. with psilocybin where a standard oral dose is approximately 10 times that of a standard intravenous dose (Carhart-Harris et al 2011).

Procedure

Screening

Prior to study enrolment, the volunteers attended a screening visit at the WTCRF. Key exclusion criteria were <21 years of age, personal history of diagnosed psychiatric illness, immediate family history of a psychotic disorder, absence of previous experience with a classic psychedelic drug (e.g. LSD, mescaline, psilocybin/magic mushrooms or dimethyltryptamine/ayahuasca), pregnancy, problematic alcohol use (i.e. >40 units consumed per week) or a medically significant condition rendering the volunteer unsuitable for the study. The decision to recruit only individuals with prior experience with psychedelics was motivated by safety considerations, i.e. to minimise the risk of an adverse response to the drug. Screening involved routine blood tests, electrocardiogram, heart rate, blood pressure and brief neurologic examination.

All participating subjects were deemed physically and mentally healthy by the study psychiatrist, and none had any history of drug or alcohol dependence or diagnosed psychiatric disorder (see 'Results' for details of participants' drug and alcohol use). Participants also completed the screenings: the Beck Depression Inventory (BDI; Beck et al. 1961), the 60-item NEO-FFI personality scale (McCrae and Costa 1987), the modified version of the Tellegen Absorption Scale (MODTAS; Jamieson 1987; Tellegen and Atkinson 1974) and the Object-Spatial Imagery and Verbal Questionnaire (OSIVQ; Blazhenkova and Kozhevnikov 2010). Participants were briefed that the purpose of the study was to ascertain an appropriate dose of LSD for a subsequent brain imaging study and that some psychological tests would be performed during the study day.

Dosing and monitoring

Volunteers attended two testing days separated by 5–7 days; placebo was administered on the first visit and LSD on the second, but the volunteers were not informed about this (single blind). Volunteers arrived at the testing centre (WTCRF) between 10:00 a.m. and 11:00 a.m. on testing days, were re-briefed about the study procedure, gave a urine test for drugs of abuse and carried out a breathalyser test for recent alcohol use. A cannula was inserted into a vein in the antecubital fossa by a medical doctor and secured it. Prior to dosing, a blood pressure measure was taken. Subsequently, volunteers were encouraged to close their eyes and relax in a reclined position before a 10-ml solution of saline alone (placebo) or containing LSD was intravenously infused over a period of 3 min. Heart rate was measured throughout the testing day and recorded at regular 1–5 min intervals for the first 45 min post-infusion, together with self-ratings of the subjective intensity of the drug effects on a scale of 0 ('no effects') to 10 ('extremely intense effects'). After the initial 45-min monitoring phase, psychological testing began, and heart rate and subjective ratings were given approximately every 30–45 min. Once the subjective effects of LSD had sufficiently subsided (i.e. typically 5–6 h post-administration of the drug), the volunteers were assessed by the study psychiatrist for suitability for discharge. The present report focuses on tests that examined suggestibility and cued mental imagery, namely the CIS (Wilson and Barber 1978) and a MIT, based on the QMI (Sheehan 1967).

The Creative Imagination Scale

The CIS is a well-validated measure of imaginative suggestibility (Barber and Wilson 1978) that was developed as an alternative to standard hypnotic suggestibility tests such as the Stanford Hypnotic Susceptibility Scale (Weitzenhoffer and Hilgard 1959) and the Barber Suggestibility Scale (Barber

and Wilson 1978) that rely on a more authoritarian administration style. Scores on the CIS correlate positively with those of established tests of hypnotic suggestibility (Hilgard 1986; McConkey et al. 1979). The CIS assesses suggestibility via 10 experimenter-read suggestions for altered subjective experience: (1) that the participant's hand is being raised by a jet of water, (2) that they are drinking refreshing water, (3) that they can hear exquisite music, (4) that they feel time is slowing down, (5) that they are re-experiencing themselves back in childhood, (6) that their arm is heavy,, (7) that their finger is becoming numb, (8) that they are eating a delicious orange, (9) that sunrays are heating their hand and (10) that they are relaxing on the shore of a beach or lake. Descriptions are typically 200–250 words in length (see the supplementary material for the complete task instructions). To administer the CIS, an experimenter (RCH) reads each suggestion to a participant who is asked to close their eyes and 'think along' with the instructions.

In the current investigation, the participant lay on a bed in a reclined position, and the experimenter sat on a chair adjacent to the participant at the head of the bed. Complete silence was maintained throughout the task, with the exception of the experimenter's voice. The 10 suggestions that comprise the CIS were split into two versions (A and B) that were balanced according to the mean 'realism/vividness' scores (0–4; see below for details of ratings) of the 217 healthy volunteers who participated into a separate validation study; specifically, the two versions both had mean scores of 2.1/4 (Wilson and Barber 1978). Suggestions 1–5 (above) comprised version A and 6–10 comprised version B. Participants received one version on their first study day and the other version on their second. Half of the sample were issued version A under LSD and half were issued version B, i.e. the pre-balanced versions were also counterbalanced across conditions. Within a single study day, five suggestions were read to the participant with brief pauses between each. On completion of the suggestions, participants were given a standardised rating form and asked to rate the vividness/realism of each of the described experiences (rated 0–4, 0="not at all the same" [as experiencing the described scenario in reality], 4="almost exactly the same [as experiencing the described scenario in reality]"). The reading of five suggestions plus the subsequent ratings took approximately 15 min.

Mental imagery test

Mental imagery has previously been assessed using the QMI (Sheehan 1967), a 35-item questionnaire that uses items/cues to elicit imagined experiences in seven different sensory modalities: (1) visual, (2) auditory, (3) olfactory, (4) tactile/touch, (5) motor/action, (6) gustatory/taste and (7) positive emotion/affect. Specifically, the participant is asked to close his/her eyes and listen to the experimenter's (RCH) description of

each item, to imagine the described item as vividly as possible and then to rate the vividness of their experience on a 7-point ordinal scale ranging from "I think of it [i.e. the described item] but do not have an image [of it] before me" to "very vivid and as clear as in reality". The QMI has been used previously in a psychopharmacology study investigating the effects of nitrous oxide on suggestibility and imagination (Whalley and Brooks 2009). In the Whalley study, the 35-item QMI was administered twice on the basis of the QMI's reasonable test-retest reliability (75 %); however, to avoid an order confound in the present fixed order design, it was considered preferable to construct two versions of a mental imagery test and then to counterbalance these across conditions (i.e. 50 % of participants completed version A on LSD and 50 % completed version B). Thus, 35 pairs of items/cues were chosen, with five addressing seven different sensory modalities, as in the QMI. Some examples include 'a train' (version A) and 'a bus' (version B) for the visual modality and 'the horn of a car' (version A) and 'a dog barking' (version B) for the auditory modality. The full list of 70 items used in the present study, as well as the complete instructions can be found in the supplementary material. The MIT was issued in a similar way to the QMI except that ratings were given orally and with eyes shut after each imagined item on a 0–6 scale, with 0 indicating that the participants had no mental image and 6 indicating that the participant's mental image was 'as clear and vivid as in reality'.

Data analysis

The primary outcome of the CIS was between-condition differences in mean CIS scores and the primary outcome of the MIT was between-condition differences in mean MIT scores. Two-tailed t tests were used to test the significance of these between-condition comparisons. In addition to analysing the overall means of MIT ratings, between-condition ratings of vividness/realism for the seven different sensory modalities assessed by the MIT were also compared (paired t tests), but these results are only presented as supplementary material. For correlational analyses, Pearson product-moment coefficients were calculated, and two-tailed hypotheses were tested. Bonferroni correction for multiple comparisons was used where appropriate.

Results

Participant demographics

Ten healthy volunteers participated in the study (one female, mean age=34.2±7.4, range=26–47). All had at least one previous experience with a classic psychedelic drug (mean

estimated LSD uses=65±90, range=0–250), but not within 21 days of the study (mean last use of LSD=1,829±2,348; range=30–5,000 days). Self-estimates of other drug use were as follows (mean, SD, range): weekly alcohol units=9.2±9.1, 0–26; daily cigarettes=3.5±6.6, 0–20; cannabis uses=822± 377, 20–1,000; MDMA uses=79±117, 3–400; psilocybin/ magic mushroom uses=19.5±14, 6–40; ketamine uses=51± 84, 0–200; and cocaine uses=23.1±31, 0–100. Beck Depression Inventory scores were 1.9±1.6, 0–4. NEO-FFI scores were the following: neuroticism=13.2±6.5, 5–26; extraversion=32±8, 20–44; openness=31±3.8, 26–35; agreeableness=35.7±4.1, 32–45; and conscientiousness=34.2±6.5, 25–42. MODTAS scores were 34.7±27.1, 46–127 and OSIVQ (visual-object subscale only) scores were 3±0.61, 2.4–4.

Effect of LSD on suggestibility

The mean score on the CIS, measuring the vividness/realism of suggested scenarios, was significantly higher for the LSD (2.75±1.2) than the placebo condition (1.8±0.7), t=2.9, df=9, p=0.018 (Cohen's d=1) (Fig. 1) (see the supplementary material for the scores for each CIS item).

Effect of LSD on cued imagery

The overall mean score on the MIT, measuring the vividness/ realism of the 35 imagined items, was higher for the LSD condition (4.3±1.25) than for the placebo condition (3.7±0.8), but this difference was not statistically significant: t=1.8, df=9, p=0.11 (Cohen's d=0.6, Fig. 2) (see the supplementary material for the scores for each of the seven modalities assessed).

Baseline predictors of cued imagery and suggestibility

Relationships between the non-clinical baseline measures (i.e. the NEO-FFI, MODTAS and OSIVQ) and the *degree of enhancement* of cued imagery and suggestibility were tested. There was a significant positive relationship between LSD enhancement of MIT scores and baseline visual imagery ability (r=0.72, r^2=0.51, n=10, p=0.02). LSD enhancement of CIS scores correlated positively with the conscientiousness subscale of the NEO-FFI (r=0.89, r^2=0.79, n=10, p=0.0005) and this strong relationship survived Bonferroni correction for testing the five NEO-FFI factors (i.e. corrected α=0.05/5=0.01) (Fig. 3).

Validity checks

To provide reassurance that the two versions of the CIS and MIT were equivalent in their capacity to elicit vivid/realistic experiences and therefore appropriately balanced for this cross-over design, the means of the two versions were compared, collapsing across conditions. There were no differences between the two versions of the tests, i.e. the mean score for version A of the CIS was 2.1±0.38 and for version B it was 2.5±0.5 (t=1.2, df=4, p=0.30) and the mean score for version A of the MIT was 4±1 and for version B it was 4±1.2 (t=0.01, df=9, p=0.99).

Discussion

Summary of main findings

This study sought to test the putative suggestibility-enhancing effects of LSD. LSD had a selective enhancing effect on
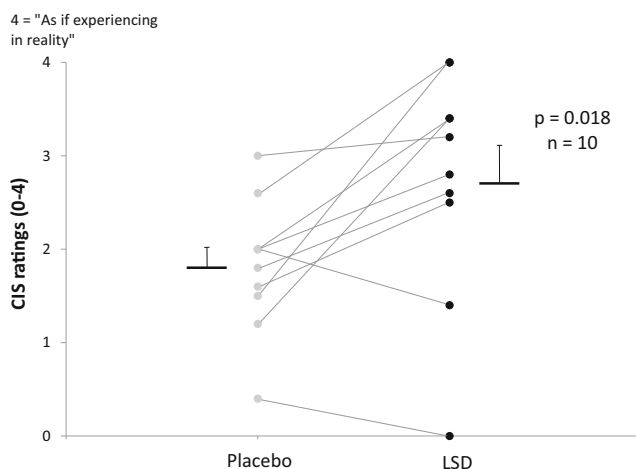

Fig. 1 Effect of LSD on suggestibility measured via the CIS. Participants scored significantly higher on the CIS on LSD than placebo (t=2.9, df=9, p=0.018, two-tailed t test). Mean values+SEM are displayed adjacent to the individual data points for each condition
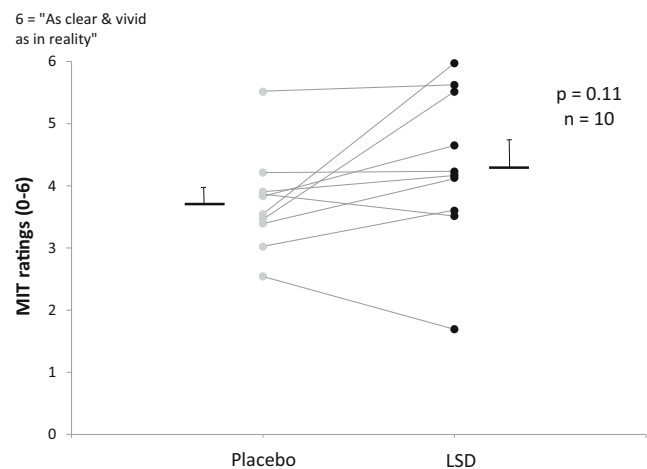

Fig. 2 Effect of LSD on cued mental imagery measured via the MIT. There was a trend towards enhanced vividness of mental imagery under LSD but the between-condition difference was not statistically significant (t=1.8, df=9, p=0.11, two-tailed t test). Mean values+SEM are displayed adjacent to the individual data points for each condition

suggestibility measured via the CIS and did not significantly enhance cued mental imagery measured by the MIT. Trait conscientiousness was positively correlated with the increase in suggestibility observed under LSD.

Implications and potential applications

Clinical research with LSD has been treated as virtually off-limits for close to half a century; however, research with psychedelics has been slowly resurrecting since the mid-1990s (Strassman and Qualls 1994), and 2014 witnessed the first report on a clinical trial with LSD since the early 1970s (Gasser et al. 2014). There is a growing belief that psychedelic drugs possess considerable untapped potential as research tools in psychology and therapeutic aids in psychiatry (Griffiths and Grob 2010; Nutt et al. 2013; Sessa 2005), but a clearer characterisation/definition of their principal effects on the mind and brain will help to demonstrate to a larger audience *why* they are important (Carhart-Harris et al. 2014). Understanding the mechanisms underlying the apparently robust suggestibility-enhancing effects of psychedelics may prove especially useful in this context.

The importance of prior expectations ('set') and environment ('setting') in determining the nature of an individual's psychedelic experience is often emphasised (Johnson et al. 2008), and this is likely to be related to these drugs' seemingly robust suggestibility-enhancing effects. Also relevant to both set and setting is the manner in which a psychedelic experience is theoretically *interpreted*. In the 1950s and 1960s, the majority of psychedelic-assisted psychotherapy adhered to a psychoanalytic/psychodynamic model (Abramson 1967; Josiah Macy and Abramson 1960), i.e. it was believed that psychedelics lower 'ego defences', thereby providing the ideal conditions for an emotional release/catharsis and personal and/or existential insight (Cohen 1964; Grof 1980; Sandison and Whitelaw 1957). It was even claimed that "Observations from LSD psychotherapy could be considered laboratory proof of the basic Freudian premises" (Grof 1980). While there may well be some substance to the psychodynamic interpretation of the psychedelic experience (Carhart-Harris et al. 2014), it is important to consider the role that suggestion plays here. For example, it was noted by therapists working with LSD in the 1950s and 1960s that patients appeared to be even more inclined than normal to endorse experiences consistent with their therapist's own theoretical allegiances, e.g. patients treated by Jungian therapists would report self-transcendent experiences under LSD, whereas those treated by Freudians would be more likely to report recollections of childhood memories (Josiah Macy and Abramson 1960). Thus, although it would be unfair to discount reports of phenomena such as 'ego dissolution' and personal and philosophical insights as mere products of suggestion, it is important to consider how the *interpretation* or *framing* of these experiences is influenced by suggestion. Similarly, the influence of suggestion in reports of psychedelic-induced mystical or religious experiences should be further investigated since the same neurobiological state may be subjectively interpreted as profound yet secular by one individual but mystical by another. Neuroimaging studies may help to inform the question of whether self-proclaimed 'mystical' experiences rest on different brain mechanisms than non-mystical experiences in the context of psychedelics.

Findings of increased suggestibility under LSD have implications beyond considerations of how the psychedelic experience is interpreted however. LSD's potential as an enhancer of mind control was heavily researched in the 1950s and 1960s, but its efficacy for this purpose was never revealed (Marks 1979). There are arguably much more positive and universally valuable applications of LSD's suggestibility-enhancing effects, however, such as in psychotherapy. Recently, completed trials investigating the utility of psychedelics in psychotherapy have appeared to be non-committal in their allegiance to any particular therapeutic model but have demonstrated safety and an impressive efficacy in treating anxiety related to dying (Gasser et al. 2014; Grob et al. 2011). Whether explicitly exploited or otherwise, the influence of suggestion is likely to have played an important role in these study's outcomes. Indeed, given the growing support for cognitive and behaviourally oriented psychotherapies, it may be interesting to isolate this as a variable in future trials to specifically investigate the influence of LSD on therapeutically motivated conditioning and deconditioning techniques, as such are used in addiction treatment for example. Such methods may supplement rather than replace the less prescriptive psychoanalytically oriented approach that encourages a patient to allow his/her inner experience to unfold 'naturally' or spontaneously.

It is important to note that there are negative and positive implications of enhanced suggestibility in the context of psychedelic-assisted psychotherapy. For example, the issue of false memory is one of the most controversial in mental health (Rosen et al 2004), and accusations of a therapist's suggestion are often made in such cases. Thus, there may be an increased danger of inducing false memories or instantiating particular beliefs in psychotherapy with psychedelics, and this matter deserves some consideration when evaluating the potential merits and pitfalls of psychedelic psychotherapy.

Neurobiological implications and theoretical considerations

LSD has affinity for and agonist properties at a number of different neurotransmitter receptors, but it is thought that its principal psychedelic effects depend on stimulation of the 5-$HT_{2A}R$ (Nichols 2004). Affinity for the 5-$HT_{2A}R$ correlates positively with the potency of different psychedelics (e.g. LSD has a particularly high affinity for the 5-$HT_{2A}R$, and

doses as low as 20 µg can produce 'psychedelic' effects) (Glennon et al. 1984), and pre-treatment with $5\text{-HT}_{2A}R$ antagonists significantly attenuate psychedelic effects of psilocybin in humans (Vollenweider et al. 1997) and behavioural indices of $5\text{-HT}_{2A}R$ signalling in rodents (Halberstadt and Geyer 2011). Potentially relevant to the present study findings, $5\text{-HT}_{2A}R$ signalling has been linked to increased cognitive flexibility (Boulougouris et al. 2008; King et al. 1974) and associative learning (Harvey 2003; Romano et al. 2010) and increased neural plasticity in the cortex (Gewirtz et al. 2002; Vaidya et al. 1997). These findings support the hypothesis that $5\text{-HT}_{2A}R$ signalling induces a state of heightened plasticity, which may be a pre-requisite for suggestibility. LSD-induced neural plasticity may be exploited therapeutically, e.g. in behavioural interventions for addiction that seek to extinguish reinforced patterns of behaviour or instate newer, 'healthier' ones.

Recent human neuroimaging studies with psilocybin have revealed decreases in large-scale brain network integrity and increases in network flexibility that may be relevant to increased suggestibility (Carhart-Harris et al. 2014; Muthukumaraswamy et al. 2013; Roseman et al. 2014; Tagliazucchi et al. 2014). It has been proposed that increased suggestibility, such as has been seen with certain drugs, may be due to the suspension of reality testing in the acute drug state, such that the individual feels less assured about his/her own beliefs and, therefore, more receptive to external direction (Sjoberg and Hollister 1965; Whalley and Brooks 2009). Supporting this hypothesis, a recent magnetoencephalography study with psilocybin found that alpha desynchrony in an important brain region (the posterior cingulate cortex, PCC) belonging to an important brain network (the default mode network) that has been hypothesised to be involved in ego functions such as reality testing (Carhart-Harris and Friston 2010) correlated strongly with participants' ratings of 'ego disintegration' (Carhart-Harris et al. 2014), i.e. the greater the desynchrony in the PCC, the more participants endorsed the statement "I experienced a disintegration of my self or ego". These findings demand further scrutiny. If it is found that drug-induced changes in default mode network activity correlate with enhanced suggestibility, then these could be treated as biological and behavioural proxies for ego integrity and used to develop the construct validity of 'the ego' and ego integrity as part of a 'neuropsychoanalytic' agenda (Carhart-Harris 2013; Carhart-Harris and Friston 2010; Carhart-Harris et al. 2014; Panksepp and Solms 2012).

Trait conscientiousness was highly predictive of subsequent increases in suggestibility under LSD (Fig. 3) that supports the model proposed above since conscientiousness is considered to be related to 'ego control' (Gelade 1997). It is intriguing therefore that those who scored highly on conscientiousness were those who were most sensitive to the suggestibility-enhancing effects of LSD, perhaps because their more conscientious tendencies implied that the drug
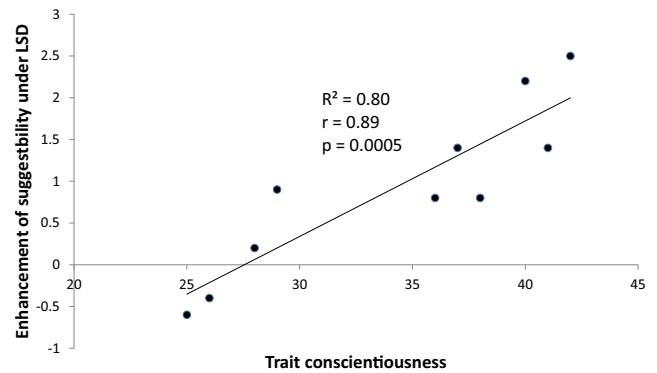

Fig. 3 Trait conscientiousness predicts sensitivity to the suggestibility-enhancing effects of LSD. Trait conscientiousness measured at screening/baseline via the NEO-FFI predicts 80 % of the variance in the difference between CIS scores under LSD versus placebo ($r=0.89$, $n=10$, $p=0.0005$)

could elicit a greater *change* in promoting the suspension of this. In future research, it may be interesting to use the 240-item, revised NEO personality inventory (NEO PI-R) rather than the 60-item version used here. The 240-item version contains 30 sub-scales within the 'big 5' that have become so synonymous with the NEO PI. Within conscientiousness, for example, there are six sub-scales: (1) sense of mastery, (2) order, (3) dutifulness, (4) achievement striving, (5) self-discipline and (6) deliberation. Thus, it would be interesting to investigate which of these is most predictive of susceptibility to LSD-enhanced suggestibility and what trait conscientiousness relates neurobiologically (e.g. high cortical serotonin 2A receptor densities/binding?).

Executive control and suggestibility

Related to the above, alterations to systems of executive control are implicated in theories of hypnotic responding. For example, some theories of hypnosis equate hypnotic responding with attenuated frontal lobe functioning and predict that if the performance of the executive system is compromised, then suggestibility proneness is likely to be enhanced (Dienes et al. 2009; Woody and Sadler 1998), whereas others hypothesise an increased role of executive functioning in responding to suggestion (Spanos, 1986; Hilgard 1986; Crawford et al. 1998). Studies using alcohol (Semmens-Wheeler et al. 2013) and transcranial magnetic stimulation (Dienes and Hutton 2013) to inhibit executive functions have begun to test these hypotheses. Psychedelic studies incorporating assessments of executive (supervisory) control could help to further inform neurobiological models of responsiveness to suggestion and hypnosis.

The effect of psychedelics on mental imagery

The present study failed to find an enhancement of mental imagery with LSD which is surprising given that enhanced

mental imagery is considered an prominent characteristic of the psychedelic state and has previously been demonstrated experimentally (Carhart-Harris et al. 2012; de Araujo et al. 2012). The specific nature of the mental imagery task employed in the present study may help to explain this discrepancy. The QMI and the modified version of it employed in the present study (i.e. the MIT) involve presenting items (i.e. usually single nouns) to participants who are instructed to rapidly imagine the sensations associated with them, e.g. "how clear and vivid can you imagine the taste of [pause]: honey [pause], an apple [pause], orange juice", etc. Participants give 0–6 ratings immediately after each item and are encouraged to "not linger too long with a specific item because a first impression is often the right one". Thus, the MIT is prescriptive in nature and demands a rapid focus of attention. Although imagery may indeed be enhanced by psychedelics (Carhart-Harris et al. 2012; de Araujo et al. 2012), a drug-induced inability to focus and respond to rapidly presented cues may counteract this effect (Carter et al. 2005; Spitzer et al. 1996). This impairment may relate to an increased semantic spread under LSD, which has previously been shown with psilocybin (Spitzer et al. 1996). Indeed, several participants reported a greater 'range' or 'repertoire' of images under LSD and that it was 'difficult to know which [image] to choose' for their rating.

It would be interesting to test the effect of LSD on mental imagery using a different task design that invites participants to take longer to produce their mental images or permits them greater autonomy in what they are allowed to imagine. One might predict that the previously demonstrated imagery-enhancing effects of psychedelics (Carhart-Harris et al. 2012; de Araujo et al. 2012) would be preserved in such a design and that response times would correlate positively with the vividness of the reported imagery.

There was a significant positive correlation between baseline imagery ability and trait absorption and between trait absorption and suggestibility (supplementary material). Trait absorption has been found to relate to the T102C polymorphism of the 5-HT$_{2A}$R, where the T/T genotype, linked to a stronger 5-HT$_{2A}$R binding potential (Turecki et al. 1999), is associated with elevated trait absorption (Ott et al. 2005). Trait absorption has been found to be predictive of the subjective effects of acutely administered psilocybin (Studerus et al. 2012). It would be interesting to test whether proneness to vivid visual imagery and suggestibility as well as their enhancement by LSD is related to the T102C polymorphism and increased 5-HT$_{2A}$R signalling, although acquiring the numbers for such an analysis would be challenging.

Limitations

This study has several limitations: It was a within-subject, placebo-controlled design, but to avoid carry-over effects from the drug to the placebo condition, LSD was always given in the second session. A balanced order design would have allayed any concern that the present results were caused by an effect of order rather than drug, but this possibility seems highly unlikely given that the CIS has previously been shown to have high test-retest reliability (Wilson and Barber 1978) and a related suggestibility scale (the Stanford Hypnotic Susceptibility Scale) and the QMI have previously been shown to be insensitive to order in a similar design with nitrous oxide (Whalley and Brooks 2009).

Another limitation is the difficulty of maintaining the blind in studies with LSD, particularly when the sample includes previous users privy to its characteristic subjective effects. This limitation could be addressed in future studies by comparing LSD against other psychoactive drugs in a within-subject design, as such was done by Sjoberg and Hollister (1965) but including non-psychedelics and variable doses to systematically test dose dependency.

The demonstrated effect of LSD on suggestibility was robust, with 80 % of participants displaying an enhancement under the drug (Fig. 1). Given the robustness of this effect and the discovery of correlations between the primary outcomes and baseline measures (e.g. Fig. 3), the study's small sample size was sufficient to detect the predicted effects. Nevertheless, a larger sample may have provided the necessary power to detect a significant effect of LSD on cued mental imagery (Fig. 2), and so the study could be considered under-powered in this respect. The recruitment of psychedelic-naïve individuals would also have extended the generalizability of the outcomes to the non-experienced population, and the recruitment of only one female precludes generalizability across genders and the possibility of examining potential gender differences.

Although 80 % of the study sample displayed some degree of enhanced suggestibility under LSD, two individuals did not (Fig. 1). Reduced suggestibility in the experimental condition is not unusual when examining change scores in such research and has been reported in comparisons between hypnotic and imaginative suggestibility (Braffman and Kirsch 1999). A similar pattern was observed in the nitrous oxide study of Whalley and Brooks (2009) where 4 out of 30 participants had lower suggestibility in the drug condition (Whalley, personal communication). It may have been relevant that the two relevant participants in the present study seemed disinclined to treat the procedure with the required formality or to view the experimenter presenting the suggestions as a figure of authority. Future studies could explore the influence of presenter style on suggestibility, e.g. by including authoritarian and non-authoritarian presenters. It would also be interesting to investigate the effects of LSD on other aspects of suggestibility such as interrogative suggestibility (Gudjonsson 1983), and it would be interesting to investigate the suggestibility-enhancing effects of LSD with functional brain imaging.

Finally, it is worth noting that the two individuals who did not show enhanced suggestibility under LSD scored lowest overall on trait conscientiousness.

Conclusions

This study demonstrated a robust enhancement of suggestibility with LSD even at moderate doses. Those most sensitive to this effect scored highest on trait conscientiousness at baseline, possibly supporting the inference that LSD facilitates suggestibility by temporarily suspending the (very human) drive to maintain control of one's mind and environment.

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