LSD alters eyes-closed functional connectivity within the early visual cortex in a retinotopic fashion

Leor Roseman[1,2*], Martin I. Sereno[3], Robert Leech[2], Mendel Kaelen[1], Csaba Orban[1], John McGonigle[1], Amanda Feilding[4], David J. Nutt[1], Robin L. Carhart-Harris[1]

[1] Centre for Neuropsychopharmacology, Department of Medicine, Imperial College London, W12 0NN London, UK

[2] Computational, Cognitive and Clinical Neuroscience Laboratory (C3NL), Department of Medicine, Imperial College London, W12 0NN London, UK

[3] Birkbeck-UCL Centre for Neuroimaging (BUCNI), WC1H 0AP London, UK

[4] The Beckley Foundation, Beckley Park, OX3 9SY Oxford, UK

*Corresponding author: Leor Roseman

Department of Medicine, Imperial College London

Hammersmith Campus, 160 Du Cane Road

London, W12 0NN

leor.roseman13@imperial.ac.uk

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ABSTRACT

The question of how spatially-organized activity in the visual cortex behaves during eyes-closed, LSD-induced "psychedelic imagery" (e.g. visions of geometric patterns and more complex phenomena) has never been empirically addressed, although it has been proposed that under psychedelics, with eyes-closed, the brain may function "as if" there is visual input when there is none. In this work, resting-state functional connectivity (RSFC) data was collected from 10 healthy subjects under the influence of LSD and, separately, placebo. It was suspected that eyes-closed psychedelic imagery might involve transient local retinotopic activation, of the sort typically associated with visual stimulation. To test this, it was hypothesised that, under LSD, patches of the visual cortex with congruent retinotopic representations would show greater RSFC then incongruent patches. Using a retinotopic localiser performed during a non-drug baseline condition, non-adjacent patches of V1 and V3 that represent the vertical or the horizontal meridians of the visual field were identified. Subsequently, RSFC between V1 and V3 was measured with respect to these a priori identified patches. Consistent with our prior hypothesis, the difference between RSFC of patches with congruent retinotopic specificity (horizontal-horizontal and vertical-vertical) and those with incongruent specificity (horizontal-vertical and vertical-horizontal) increased under LSD relative to placebo ($p=0.0017$, 1-tail, Cohen's $d=1.6$), suggesting that activity within the visual cortex becomes more dependent on its intrinsic retinotopic organization in the drug condition. This result indicates that under LSD, with eyes-closed, the early visual system behaves as if it were seeing spatially localized visual inputs.

SIGNIFICANCE STATEMENT

It is known that the spatial organisation of activity within the visual cortex reflects the intrinsic spatial properties of the world it processes. The present study addresses the question of whether eyes-closed LSD-induced psychedelic “visions” or imagery are processed in a similar way. Using fMRI, the present analysis suggests that LSD-induced eyes-closed psychedelic imagery does indeed arise when the visual cortex behaves in a similar manner to how it does during visual stimulation.

INTRODUCTION

Lysergic acid diethylamide (LSD) is a psychedelic drug and classic hallucinogen. Psychedelics have many interesting psychological effects; however, their potent hallucinogenic properties have long been a matter of scientific intrigue. Studying mescaline in the mid-1920s, Heinrich Klüver sought to document the peculiar geometric patterns that occur during intoxication with this particular compound (Klüver, 1942). Later, Jack Cowan and colleagues proposed a mechanism by which such patterns could be perceived that was based on aberrant excitation within the visual cortex and its own particular spatial architecture (Ermentrout and Cowan, 1979; Bressloff et al., 2002). Although, it has proved difficult to empirically test Cowan's model, the notion that hallucinogens induce aberrant dynamics within the visual cortex has received empirical support. For example, decreased alpha power has been observed in occipital areas with psilocybin (Kometer et al., 2013; Muthukumaraswamy et al., 2013), ayahuasca (Riba et al., 2004; Schenberg et al., 2015) and LSD (Rodin and Luby, 1966; Roseman et al., 2015), and alpha suppression was found to be predictive of the occurrence of complex psychedelic imagery (Shirahashi, 1960). Suppressed occipital alpha power is a hallmark of the eyes-closed to eyes-open transition, as is BOLD activation within the visual cortex (Goldman et al., 2002). Elevated BOLD activation in the visual cortex during the induction of eyes-closed visual-imagery has been seen in studies with ayahuasca (de Araujo et al., 2012) and psilocybin (Carhart-Harris et al., 2012) and recently we observed significant increases in resting-state functional connectivity (RSFC) between visual networks and higher-level associative networks with psilocybin (Roseman et al., 2014). Furthermore, under LSD, increased RSFC between primary visual cortex and higher-level associative areas, and increased cerebral blood flow (CBF) in visual areas, correlated

with subjective ratings of visual hallucinations, as did decreased occipital alpha power (Roseman et al., 2015).

The organization of the visual cortex is such that the visual field is represented several times in the occipital cortex with a topographic organization (Hubel and Wiesel, 1977; Zeki, 1978; Hubel and Livingstone, 1987). Topographic or retinotopic organization means that nearby regions in the retina project to nearby cortical regions (Tootell et al., 1988). By presenting videos of rotating wedges or expanding rings it is possible to map brain areas that show activity that is dependent on the spatial location of the stimulus. This technique has helped in identifying the borders between neighboring visual regions (e.g. V1, V2, V3) (Sereno et al., 1995). Furthermore, this technique can be used to identify patches within each of the visual subregions that correspond to different spatial locations or orientations (e.g. horizontal vs. vertical spatial specificity). Data obtained from retinotopic mapping has proved useful for understanding spontaneous ("resting-state") activity within the visual system (Kenet et al., 2003). Moreover, given the involvement of retinotopically-sensitive regions in the processing of spatial information, studying their spontaneous activity during resting-state conditions, with and without LSD, may produce insights into mechanisms underlying the emergence of psychedelic imagery.

The present study modified a previously used paradigm (Nir et al. (2006) to focus on activity in retinotopically sensitive patches of the lower-level visual cortex, i.e. discrete patches within V1 and V3 that are sensitive to visual stimuli presented in the horizontal and vertical planes. Broadly consistent with previously described effects of visual stimulation and imagery (Nir et al. 2006), we predicted that RSFC between retinotopically-sensitive patches within V1 and V3 that possess congruent retinotopic sensitivity (i.e. V1 horizontal - V3

horizontal or V1 vertical- V3 vertical) would be greater than RSFC between incongruent patches (e.g. V1 horizontal – V3 vertical) under LSD, but not under placebo. That is, the impact of LSD on spontaneous activity within retinotopically sensitive patches of V1 and V3 would be consistent with what one would expect from visual stimulation (Nir et al., 2006).

MATERIALS AND METHODS

Design

Twenty healthy participants (4 females) attended two scanning days (LSD and placebo) at least two weeks apart in a balanced order, within-subjects design. Two eyes-closed resting-state BOLD scans totalling 14 minutes were completed 135 minutes post infusion (75µg in 10ml saline given over 1 min) or placebo (10ml saline). Participants carried out VAS-style ratings after each scan using button press to rate the intensity of simple and complex visual hallucinations. Furthermore, the 11 factor altered states of consciousness (ASC) questionnaire (Studerus et al., 2010) was completed at the end of each dosing day. All participants reported closed-eyes psychedelic imagery (Roseman et al., 2015).

Anatomical Scans

Imaging was performed on a 3T GE HDx system. These were 3D fast spoiled gradient echo scans in an axial orientation, with field of view = 256 × 256 × 192 and matrix = 256 × 256 × 192 to yield 1mm isotropic voxel resolution. TR/TE = 7.9/3.0ms; inversion time = 450ms; flip angle = 20°.

BOLD fMRI Data Acquisition

Two BOLD-weighted fMRI data were acquired, for each condition, using a gradient echo planer imaging sequence, TR/TE = 2000/35ms, field-of-view = 220mm, 64 × 64 acquisition matrix, parallel acceleration factor = 2, 90° flip angle. Thirty-five oblique axial slices were acquired in an interleaved fashion, each 3.4mm thick with zero slice gap (3.4mm isotropic voxels). The precise length of each of the BOLD scans was 7:20 minutes.

BOLD Pre-processing

Three different but complementary imaging software packages were used to analyse the fMRI data. Specifically, FMRIB Software Library (FSL) (Smith et al., 2004), AFNI (Cox, 1996) and Freesurfer (Dale et al., 1999) were used. One subject did not complete the BOLD scans due to anxiety and an expressed desire to exit the scanner. Four others were discarded from the group analyses due to excessive head movement as measured using frame-wise displacement (FD) (Power et al., 2014). The criterion for exclusion was subjects with >15% scrubbed volumes when the scrubbing threshold is FD = 0.5. After discarding these subjects we reduced the threshold to FD = 0.4. The mean between-condition difference in mean FD for the 4 subjects that were discarded was 0.323±0.254. Four more subjects were discarded due to imperfect identification of horizontal and vertical retinotopic patches of V3. For the 11 subjects (3 females) that were used in the analysis, the difference (LSD-Placebo) in mean FD was 0.054 ±0.029 ($p = 0.0001$). Therefore, many pre-processing stages were considered with respect to the difference in head motion and these are detailed below.

The following pre-processing stages were performed: 1) removal of the first three volumes; 2) de-spiking (3dDespike, AFNI); 3) slice time correction (3dTshift, AFNI); 4) motion correction (3dvolreg, AFNI) by registering each volume to the volume most similar, in the least squares sense, to all others (in-house code); 5) brain extraction (BET, FSL); 6) rigid

body registration to anatomical scans (nine subjects with FSL's BBR, one subject with Freesurfer's bbregister and one subject manually); 7) scrubbing (Power et al., 2014) - using an FD threshold of 0.4 (the mean percentage of volumes scrubbed for placebo and LSD was 0.4 ±0.9% and 2.1 ±2.6%, respectively). The maximum number of scrubbed volumes per scan was 7.1%). Scrubbed volumes were replaced with the mean of the surrounding volumes. Additional pre-processing steps included: 8) band-pass filtering between 0.01 to 0.08 Hz (3dFourier, AFNI). Lowpass filter of 0.08 Hz is suggested to improve motion related artifacts (Satterthwaite et al., 2013); 9) linear and quadratic de-trending (3dDetrend, AFNI); 10) regressing out 9 nuisance regressors: out of these, 6 were motion-related (3 translations, 3 rotations) and 3 were anatomically-related (not smoothed). All nuisance regressors were bandpassed filtered with the same filter as in step 10. Specifically, the anatomical nuisance regressors were: I) ventricles (Freesurfer, eroded in 2mm space), II) draining veins (DV) (FSL's CSF minus Freesurfer's Ventricles, eroded in 1mm space) and III) local white matter (WM) (FSL's WM minus Freesurfer's subcortical grey matter (GM) structures, eroded in 2mm space). Regarding local WM regression, AFNI's 3dLocalstat was used to calculate the mean local WM time-series for each voxel, using a 25mm radius sphere centred on each voxel. Local WM regression has been suggested to perform better than global WM regression (Jo et al., 2013) and is considered a promising approach to deal with motion related artifacts (Power et al., 2015).

Retinotopic localizer

Subjects were presented with a 4:24 min video that alternated between vertical and horizontal polar angles (8 cycles, resolution=1400 x 1050, visual angle =23 x 23°, TR/TE=2000/25ms, 3mm isotropic voxels). The wedge consisted of a coloured checkerboard with superimposed moving black and white faces (from FERET database (Phillips et al., 1998)) and coherently

moving white dots - new flow every 0.5 second. Fourier analysis with two distinct conditions was performed on the placebo data to identify activity corresponding to the vertical and horizontal polar angles (Sereno et al., 1995). Borders between V1, V2 and V3 were identified manually for each subject (using an in-house program). The vertical meridian served as the border between V1 and V2 and the horizontal meridian served as the border between V2 and V3. Furthermore, subregions of V1 and V3 were identified based on the BOLD activity that corresponded to the vertical and horizontal polar angles; both V1 and V3 were divided into patches corresponding to the vertical and horizontal orientations ($V1_{hor}$, $V1_{ver}$, $V3_{hor}$, $V3_{ver}$).

V1-V3 Retinotopic Coordination

Horizontal and vertical retinotopic patches of V1 and V3 were identified using the retinotopic mapping described above. Mean time-series for $V1_{hor}$, $V1_{ver}$, $V3_{hor}$, $V3_{ver}$ ($_{hor}$ = horizontal orientation, $_{ver}$ = vertical orientation) were derived from each scan in native space. All results were averaged across the two resting-state scans. Parameter estimates (β) of linear regression were calculated between $V1_{hor}$ - $V3_{hor}$ (β_{hor_hor}), $V1_{hor}$ - $V3_{ver}$ (β_{hor_ver}), $V1_{ver}$ - $V3_{hor}$ (β_{ver_hor}), $V1_{ver}$ - $V3_{ver}$ (β_{ver_ver}). Retinotopic Coordination (Figure 1A) was calculated as follows:

$$Retinotopic\ Coordination = \beta_{hor\_hor} + \beta_{ver\_ver} - \beta_{hor\_ver} - \beta_{ver\_hor}$$

One subject was identified as an outlier and was not included in the analysis (based on the Outlier Labelling Rule with g=2.2 (Hoaglin et al., 1986)).

RESULTS

V1-V3 Retinotopic Coordination

The mean values for retinotopic coordination (i.e. the difference in RSFC between retinotopically congruent patches and incongruent patches) for placebo and LSD were -0.005±0.029 and 0.068±0.058, respectively ($p=0.0018$, 1-tail, paired t-test, Cohen's $d=1.6$) (boxplot is presented in Figure 1B). Retinotopic Coordination for each subject and for each condition, are shown in Figure 1C. This result is based on the mean of the two resting-state scans (each condition had two separate scans) but it was also significant for each of the resting-state scans alone ($p=0.0288$ and $p=0.0057$). Furthermore, the results showed the same trend for the right and left hemispheres separately ($p = 0.022$ and $p = 0.078$, respectively). Importantly, the increased retinotopic coordination did not correlate with increased head motion under LSD ($p = 0.99$, 1-tail) but neither did it correlate with rating scales of psychedelic imagery.

DISCUSSION

The present study found that LSD modulated RSFC within the visual cortex in a manner that reflects its intrinsic retinotopic architecture, i.e. RSFC between patches of V1 and V3 that possess a congruent retinotopic representation was stronger than RSFC between patches possessing incongruent retinotopic representations. Consistent with previous studies (Carhart-Harris et al., 2012; de Araujo et al., 2012) these findings suggest that psychedelics modulate activity within the visual cortex "as if" there were an external visual input.

Interpretation of the present results regarding psychedelic imagery may be informed by more general research on visual imagery (Pylyshyn, 2002; Kosslyn et al., 2006). A key question in this research area is whether low-level processors of the visual system (e.g. the primary visual cortex) contribute to the representation of complex mental images (de Gelder et al., 2014; Pearson and Kosslyn, 2015). A similar debate is still on-going regarding rapid eye movement (REM) sleep, i.e., it is not clear whether the primary visual cortex is engaged (Hong et al., 2009; Miyauchi et al., 2009) or disengaged (Braun et al., 1998) during REM sleep. The present study's analyses address a related question but in this case concerning eyes-closed psychedelic imagery rather than dream imagery or visual imagery more generally and our findings imply that low-level components of the visual system (i.e. retinotopically-sensitive regions within V1 and V3) are indeed modified under LSD. Moreover, our results suggest that under LSD, the early visual system behaves "as if" it were receiving spatially localized visual information.

Early electrophysiological studies involving psychedelics (chiefly LSD) reported altered activity in the retina (Apter and Pfeiffer, 1956; Mouriz-Garcia et al., 1969), LGN (Phillis et

al., 1967; Walter et al., 1971; Morgane and Stern, 1972) and visual cortex (Evarts et al., 1955) under these drugs. However, the nature of altered neural activity in the visual cortex appears to be strongly dose-dependent (Dray et al., 1980) and these studies say little about the functional implications of the relevant effects. The merit of the present study is that it directly addressed how activity within low-level aspects of the visual system is altered under a psychedelic (i.e. that V1 and V3 show increased retinotopic coordination under LSD) and what this means on a functional level (i.e. that the brain is behaving "as if" there is visual input under the drug).

A limitation of the present study is that the increased retinotopic coordination within V1 and V3 under LSD did not correlate with ratings of visual hallucinations. One explanation for this is that increased retinotopic coordination reflects a specific alteration in the spatial properties of psychedelic imagery and not its general intensity. For example, while the overall intensity of the hallucinatory experience may increase (e.g. with a higher dose of LSD) the psychedelic imagery may lose some of its spatial properties and this would relate to a decrease rather than an increase in retinotopic coordination. This matter could be addressed by including a different measure of the hallucinatory experience that enquires specifically about the spatial vividness of the psychedelic imagery, as well as its location in space. We would predict that psychedelic visions that are especially sharp or vivid and clearly located in space would relate to an increase in retinotopic coordination. Another possible explanation for the lack of correlation between the subjective intensity of the psychedelic imagery and the reported RSFC results is that higher levels of motion interfered with accurate measurements of retinotopic coordination: indeed, subjects that had higher differences (LSD-placebo) in head motion had a lower difference in retinotopic coordination, i.e. head motion "diluted" the main drug effect on retinotopic coordination.

Another limitation of this study is the small sample size (N=10). Unfortunately, psychedelic neuroimaging studies are sensitive to data loss issues, mainly related to high levels of head motion associated with the drug condition. Future studies should take this into account and collect more data than would ordinarily be needed in order to compensate for potential data loss. Even with motion considered however, we had a very clear prior hypothesis that proved correct in 9 out of the 10 subjects and post-hoc analyses indicated that head motion had a deleterious rather than a contributory influence on this predicted effect.

In conclusion, the present study's results suggest that under the influence of LSD, the visual cortex acts as if it is processing spatially localized visual information. However, further work is required to investigate the specific regional source/s of eyes-closed psychedelic imagery, e.g. does it arise purely from changes localised to the early visual cortex, or are there upstream or downstream regions also implicated? More work is also required to identify associations between the subjective quality of psychedelic imagery and underlying changes in brain activity. These investigations should help to inform on the function of the visual system during normal conditions and how this can go awry in certain abnormal states.

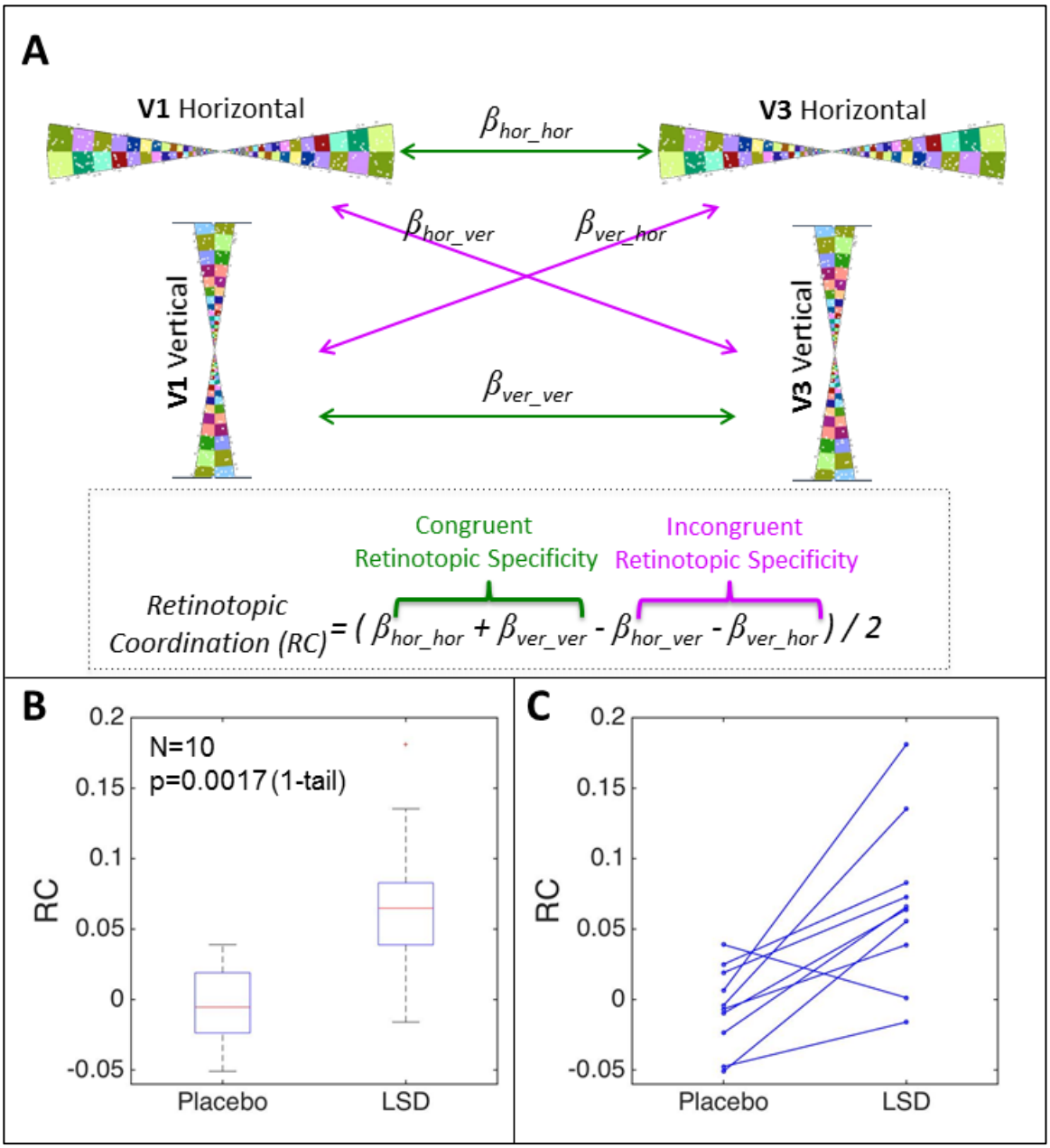

Figure 1. Changes in Retinotopic Coordination (RC) between V1 and V3 under LSD or Placebo. A) Calculating RC for each subject for each condition. Horizontal and vertical patches of V1 and V3 were identified using a retinotopic localiser. Four regressions between patches of V1 and V3 produced four regression coefficients (β values) that represent the strength of RSFC. RC was calculated by adding the β values of patches with the congruent retinotopic specificity and then subtracting the β values of patches with incongruent retinotopic specificity. B) Boxplot of RC for Placebo and LSD. C) RC for all 10 subjects for Placebo and LSD.

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