Neuropharmacology 142 (2018) 263–269

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression

Leor Roseman [a, b, *], Lysia Demetriou [c, d], Matthew B. Wall [c], David J. Nutt [a], Robin L. Carhart-Harris [a]

[a] Psychedelic Research Group, Centre for Psychiatry, Department of Medicine, Imperial College London, W12 0NN London, UK
[b] C3NL, Department of Medicine, Imperial College London, W12 0NN London, UK
[c] Imanova, Centre for Imaging Sciences, W12 0NN London, UK
[d] Investigative Medicine, Department of Medicine, Imperial College London, W12 0NN London, UK

ARTICLE INFO

Article history:
Received 18 July 2017
Received in revised form
20 September 2017
Accepted 22 December 2017
Available online 27 December 2017

Keywords:
Psilocybin
Psychedelics
Depression
Amygdala
fMRI
Emotional processing

ABSTRACT

Recent evidence indicates that psilocybin with psychological support may be effective for treating depression. Some studies have found that patients with depression show heightened amygdala responses to fearful faces and there is reliable evidence that treatment with SSRIs attenuates amygdala responses (Ma, 2015). We hypothesised that amygdala responses to emotional faces would be altered post-treatment with psilocybin. In this open-label study, 20 individuals diagnosed with moderate to severe, treatment-resistant depression, underwent two separate dosing sessions with psilocybin. Psychological support was provided before, during and after these sessions and 19 completed fMRI scans one week prior to the first session and one day after the second and last. Neutral, fearful and happy faces were presented in the scanner and analyses focused on the amygdala. Group results revealed rapid and enduring improvements in depressive symptoms post psilocybin. Increased responses to fearful and happy faces were observed in the right amygdala post-treatment, and right amygdala increases to fearful versus neutral faces were predictive of clinical improvements at 1-week. Psilocybin with psychological support was associated with increased amygdala responses to emotional stimuli, an opposite effect to previous findings with SSRIs. This suggests fundamental differences in these treatments' therapeutic actions, with SSRIs mitigating negative emotions and psilocybin allowing patients to confront and work through them. Based on the present results, we propose that psilocybin with psychological support is a treatment approach that potentially revives emotional responsiveness in depression, enabling patients to reconnect with their emotions.

Trial registration: ISRCTN, number ISRCTN14426797.

This article is part of the Special Issue entitled 'Psychedelics: New Doors, Altered Perceptions'.

© 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Psychedelic therapy is a re-emerging paradigm in psychiatry (dos Santos et al., 2016; Mithoefer et al., 2016). Unlike other psychopharmacological treatment models that seek to medicate patients on a chronic basis, the psychedelic model seeks to treat core psychological issues via a small number of profound and potentially transformative psychological experiences (Pahnke et al., 1970; Watts et al., 2017). Our recent open-label study of psilocybin with psychological support for treatment-resistant depression (TRD) yielded promising results, with all patients showing some reduction in depressive symptoms at 1 week and half meeting criteria for remission at 3 weeks (Carhart-Harris et al., 2017). Furthermore, other clinical studies with psilocybin have found reductions in anxiety and depressive symptoms after psilocybin with psychological support (Griffiths et al., 2016; Ross et al., 2016).

Psilocybin, a classic psychedelic and non-selective serotonin 2A receptor (5-HT2AR) agonist, was discovered and marketed in the 1950s and 60s (Hofmann et al., 1958). After much early enthusiasm about the therapeutic potential of psychedelics (Grinspoon and Bakalar, 1979; Rucker et al., 2016), a politically-led about-turn in the mid-1960s and early 1970s effectively ended all research with these drugs, and it has only been in the last 10–15 years that clinical

* Corresponding author. Centre for Psychiatry, Department of Medicine, Imperial College London, 160 Du Cane Road, W12 0NN London, UK.
E-mail address: leor.roseman13@imperial.ac.uk (L. Roseman).

https://doi.org/10.1016/j.neuropharm.2017.12.041
0028-3908/© 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

researchers have begun to work with them again. During this renascent period, impressive results have been found for the treatment of depression (Carhart-Harris et al., 2016; Osório et al., 2015), end of life anxiety (Gasser et al., 2014a; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), obsessive compulsive disorder (Moreno et al., 2006) and addiction (Bogenschutz and Johnson, 2016).

The amygdala has previously been implicated in the pathophysiology of depression (Drevets et al., 1992) as well as the action of some antidepressants (Ma, 2015) and psychedelics (Kraehenmann et al., 2015; Spain et al., 2015). The amygdala is a complex subcortical structure that is sensitive to emotional stimuli (Janak and Tye, 2015; Sergerie et al., 2008). Functional MRI studies of untreated clinically depressed patients have found amygdala hyper-sensitivity to negative emotional stimuli (Drevets et al., 1992; Ma, 2015), and treatment with SSRIs has been found to attenuate this; both with chronic SSRI-use as well as early in treatment, prior to the appearance of clinical improvements (Godlewska et al., 2012).

Here, we sought to explore the antidepressant action of psilocybin on amygdala responses to emotional faces using a functional magnetic resonance imaging (fMRI) paradigm that has been well-validated in the context of SSRI-based treatments for depression (Ma, 2015). Patients underwent balanced versions of an emotional faces paradigm before and one-day after treatment with psilocybin. Psilocybin has been found to be associated with improved mood in the sub-acute period days after exposure (Majić et al., 2015). We therefore predicted that amygdala responses to emotional faces would be altered post-treatment and that this might relate to changes in depression severity. We were particularly interested in the fearful versus neutral faces contrast, due to previous findings of reduced amygdala responses to negative emotional stimuli with SSRIs (Ma, 2015). We also predicted that the nature of the acute psychological experience under psilocybin would relate to the post-treatment changes in amygdala responses.

2. Material and methods

This trial received a favourable opinion from the National Research Ethics Service London—West London, was sponsored and approved by Imperial College London and by the UK MHRA. All participants provided written informed consent.

2.1. Design

The full study procedure is reported in (Carhart-Harris et al., 2016). The inclusion criteria were major depression of a moderate to severe degree (16 + on the 21-item Hamilton Depression Rating scale [HAM-D]), and no improvement despite two adequate courses of antidepressant treatment (6 weeks minimum, each). The patients were asked to be antidepressants-free for at least two weeks before the study. Exclusion criteria were: current or previously diagnosed psychotic disorder; immediate family member with a diagnosed psychotic disorder; medically significant condition rendering unsuitability for the study; history of serious suicide attempts (requiring hospitalisation); history of mania; blood or needle phobia; positive pregnancy test at screening or during the study; and current drug or alcohol dependence. Psilocybin was obtained from THC-pharm (Frankfurt, Germany) and formulated into the investigational medicinal product (5 mg psilocybin in size 0 capsules). A week before the psilocybin session, patients attended a preparatory session with their therapists. In this session patients were invited to talk openly about their personal history (including thoughts on the origins of their depression), discussed psilocybin's psychological effects, and simulated aspects of the dosing session itself, such as listening to a sample of the session music while wearing eyeshades. The preparatory session typically lasted for 4 h, with lunch and breaks provided. The sessions took place in a decorated room with a relaxed atmosphere. The rationale behind the first low dose session was to prepare patients to the high dose, build rapport with the therapists, and test their willingness to "let-go". Twenty Patients underwent two psilocybin-assisted therapy sessions, a week apart. The first involved a low (test) dose of psilocybin (10 mg, p.o.), and the second, a higher (therapeutic) dose (25 mg, p.o). The high dose is comparable to the effective clinical psilocybin doses used in Griffiths et al. (2016) (22 or 30 mg/70 kg) and Ross et al. (2016) (0.3 mg/kg). The low dose produces attenuated but still discernible perceptual and subjective effects (Griffiths et al., 2011). The rationale behind the low dose session was as a preparation for the high dose session, providing an opportunity to build rapport with the therapists and help to reduce anxiety for the high dose session. Post capsule ingestion, patients lay with eyes closed while listening to music. Two therapists adopted a non-directive, supportive approach. Baseline fMRI scanning was conducted prior to any psychological or pharmacological interventions and the post treatment fMRI scan occurred the morning after the high dose psilocybin session, prior to any psychological integration work. Scanning sessions took place at identical times of the day (i.e. 10:00am). Out of the initial 20 patients, 19 completed both scanning sessions (6 females; mean age = 44.7 ± 10.9; 27 to 64).

2.2. Anatomical scans

Imaging was performed on a 3T Siemens Tim Trio using a 12-channel head coil at Imanova, London, UK. Anatomical images were acquired using the ADNI-GO (Jack et al., 2008) recommended MPRAGE parameters (1 mm isotropic voxels, TR = 2300ms, TE = 2.98ms, 160 sagittal slices, 256 × 256 in-plane FOV, flip angle = 9°, bandwidth = 240 Hz/pixel, GRAPPA acceleration = 2).

2.3. BOLD fMRI emotional faces images task

T2*-weighted echo-planar images (EPI) were acquired for the functional scan using 3 mm isotropic voxels, TR = 2000ms, TE = 31ms, 36 axial slices, 192 mm in-plane FOV, flip angle = 80°, bandwidth = 2298 Hz/pixel, GRAPPA acceleration = 2, number of volumes = 245. Patients used a mirror mounted on the head-coil to view a screen mounted in the rear of the scanner bore, where visual stimuli were back-projected through a wave-guide in the rear wall of the scanner room. The emotional faces task was a block-design task lasting 8 min. Patients were shown faces with either fearful, happy, or neutral expressions, selected from the Karolinska Directed Emotional Faces set (Goeleven et al., 2008). An equal number of male and female faces were selected for the task. Each face was presented on screen for 3 s, and five faces of the same expression were presented in each 15 s block. Rest blocks (also 15 s) were also included, and there were 8 repetitions of each block type, presented in a pseudo-random sequence (32 blocks in total). Two versions of the task were used with one presenting blocks in the reverse order to the other. Order of the task versions on each scanning visit was counter-balanced across patients. Patients passively viewed the faces but were instructed to press a single button with their thumb with the presentation of each new face, to confirm that they were paying attention to the stimuli.

2.4. BOLD pre-processing

Four 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), Freesurfer (Dale et al., 1999) and Advanced Normalization Tools (ANTS) (Avants et al., 2009) were used. The following pre-processing stages were performed: 1) motion correction (3dvolreg, AFNI) by registering each volume to the volume most similar, in the least squares sense, to all others (in-house code); 2) brain extraction (BET, FSL); 3) rigid body registration to anatomical scans (BBR, FSL); 4) non-linear registration to 2 mm MNI brain (Symmetric Normalization (SyN), ANTS); 5) scrubbing (Power et al., 2012) – using a framewise displacement (FD) threshold of 0.90 mm, which is a recommended threshold for task fMRI (Siegel et al., 2014). No significant difference in head movement (mean FD) was found between before and after therapy scans (0.243 mm ± 0.116 and 0.248 mm ± 0.12, respectively, $p = .815$). The mean percentage of scrubbed volumes across subjects ($n = 19$) for the before scan was 2.3% ± 3.7 (range = 0–15.1%), and for the after scan, it was 2.3% ± 3.3 (range = 0–11.8%). Scrubbed volumes were replaced with the mean of the surrounding volumes; 6) spatial smoothing (FWHM) of 6 mm (3dBlurInMask, AFNI); 7) high-pass filter of 0.01Hz; 8) regressing out 6 motion-related nuisance regressors (3 translations, 3 rotations, high-pass filtered with the same 0.01Hz filter).

2.5. ROI analysis

We used two different approaches to investigate changes of amygdala activity. The first involved calculating mean amygdala signal of left and right amygdala ROIs. The second involved voxelwise analysis within a bilateral amygdala mask (Harvard-Oxford atlas, probability > 50%). For both approaches, a standard General Linear Model (GLM) was used for the first analysis step, as implemented in the FEAT module in FSL. Regressors derived from the onset times of each stimulus condition were convolved with a Gamma function in order to simulate the Haemodynamic Response Function (HRF). Pre-whitening (FILM) was applied to correct for autocorrelations. Contrasts were defined that isolated activity related to each stimulus condition (fearful, happy, neutral) relative to the baseline, and also compared between two stimulus conditions, as appropriate (fearful > neutral and happy > neutral) (Five contrasts in total). Two-tailed t-tests were performed to compare before versus after treatment (before any intervention and after the high dose) BOLD responses for the mean ROI analysis and mixed-effects GLM (FLAME-1+2) for the voxelwise analysis. A statistical threshold of $Z > 2.3$, (cluster-corrected for multiple comparisons with $p < .05$) was used for all voxelwise analyses. A further voxelwise exploratory analysis was carried out on the whole brain.

2.6. Relationship with clinical outcomes

The relationships with clinical outcomes were observed using voxelwise analysis within a right amygdala mask (only the right amygdala was chosen based on the first level results). For each subject, a fixed-effects analysis was conducted to calculate the difference between before versus after therapy (before any intervention and after the high dose). A higher level mixed-effects GLM (FLAME 1 + 2) was used with the relevant clinical outcome as a regressor of interest. In order to avoid multiple comparisons, we chose only two clinical outcomes of interest: 1) the self-rated Beck Depression Inventory (BDI) 1-week after therapy, criterion for *remission* was ≤ 9, which is based on a cut-off by Beck et al. (1988), and criterion for treatment *response* was 50% reduction from baseline – a consensus which has been validated by Riedel et al. (2010); and 2) treatment *response* (50% reduction) based on in-scanner 'state' rating (0–20) of depressed mood (baseline (before treatment) compared with one-day after treatment). The in-scanner ratings were taken immediately after the faces task and thus, sample the depressed 'state' (compared to the BDI which asks about the last two weeks). After viewing the imaging results we decided to use *post-hoc* the Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 2003) at 1-day (concerning only the time since the therapy session), 1-week, 2-weeks, 3-weeks, and 5-weeks post-treatment. We chose to use QIDS as an extra scale to measure depression and to strengthen the relationship between changes in the amygdala and depression. QIDS was measured in more time pointes then BDI and therefore allowed us to observe how changes in the amygdala predict clinical outcomes in different time points. Furthermore, as reduced anxiety was an important clinical outcome in other psilocybin studies (Griffiths et al., 2016; Ross et al., 2016), we looked also at relationship between anxiety and amygdala changes. Anxiety was measured at the day of the scan using the in-scanner rating, and 1 week after the scan using State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970).

3. Results

3.1. ROI analysis

Increased post-treatment BOLD responses were observed in the right amygdala for fearful ($p = .001$) and happy faces ($p = .022$), with a trend effect for neutral faces ($p = .066$) (Fig. 1). After correcting for 10 tests (5 contrasts X 2 ROIs), only the increased responses to fearful faces remained significant. No significant result was observed in the left amygdala ($p = .11$, $p = .95$ and $p = .2$, for fearful, happy and neutral faces, respectively). Voxelwise analysis revealed significantly greater responses in the right amygdala post-treatment for four contrasts: fearful, happy and neutral faces, plus fearful > neutral faces (Fig. 2). Increases were in a consistent location of the right amygdala.

3.2. Whole brain analysis

Whole brain analysis (Fig. 3) revealed that for the fearful,

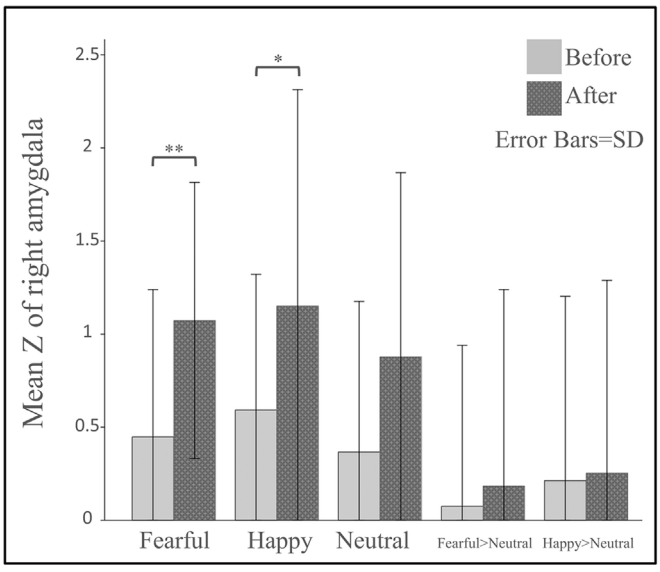
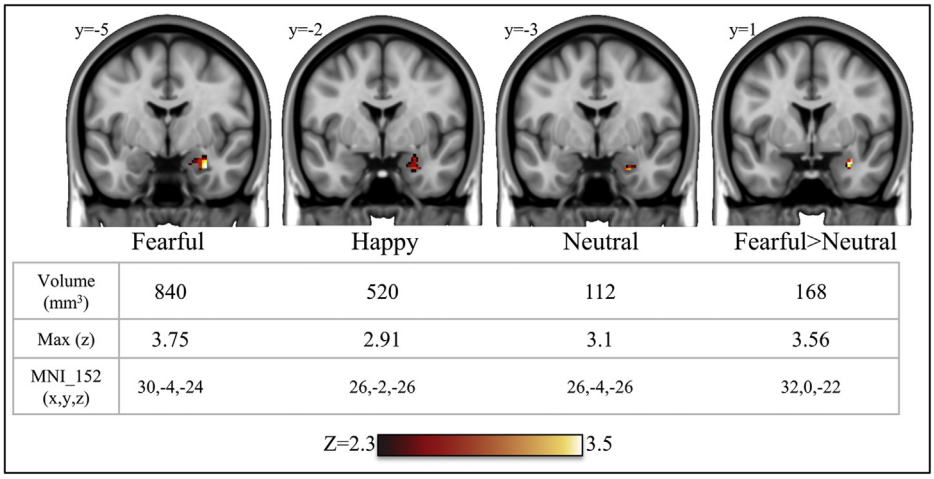


Fig. 1. Mean Z values of BOLD activation in right amygdala for different stimuli conditions, before and after psychedelic-assisted therapy. Increased amygdala responsivity is observed for both fearful and happy faces. No significant result was found for left amygdala. Error Bars = Standard Deviation
* $p < .05$ (2-tail *t*-test, uncorrected)
** $p < .05$ (2-tail *t*-test, Bonferonni correction for 10 comparisons (5 contrasts X 2 ROIs).



	Fearful	Happy	Neutral	Fearful>Neutral
Volume (mm^3)	840	520	112	168
Max (z)	3.75	2.91	3.1	3.56
MNI_152 (x,y,z)	30,-4,-24	26,-2,-26	26,-4,-26	32,0,-22

Fig. 2. Voxelwise increases within right amygdala mask (after > before therapy). Significant clusters within right amygdala that showed increased responsivity after therapy. Cluster size and Max point are presented as well. Note that for all four contrasts the cluster is located in a similar location. All results are cluster corrected ($z > 2.3$, $p < .05$).

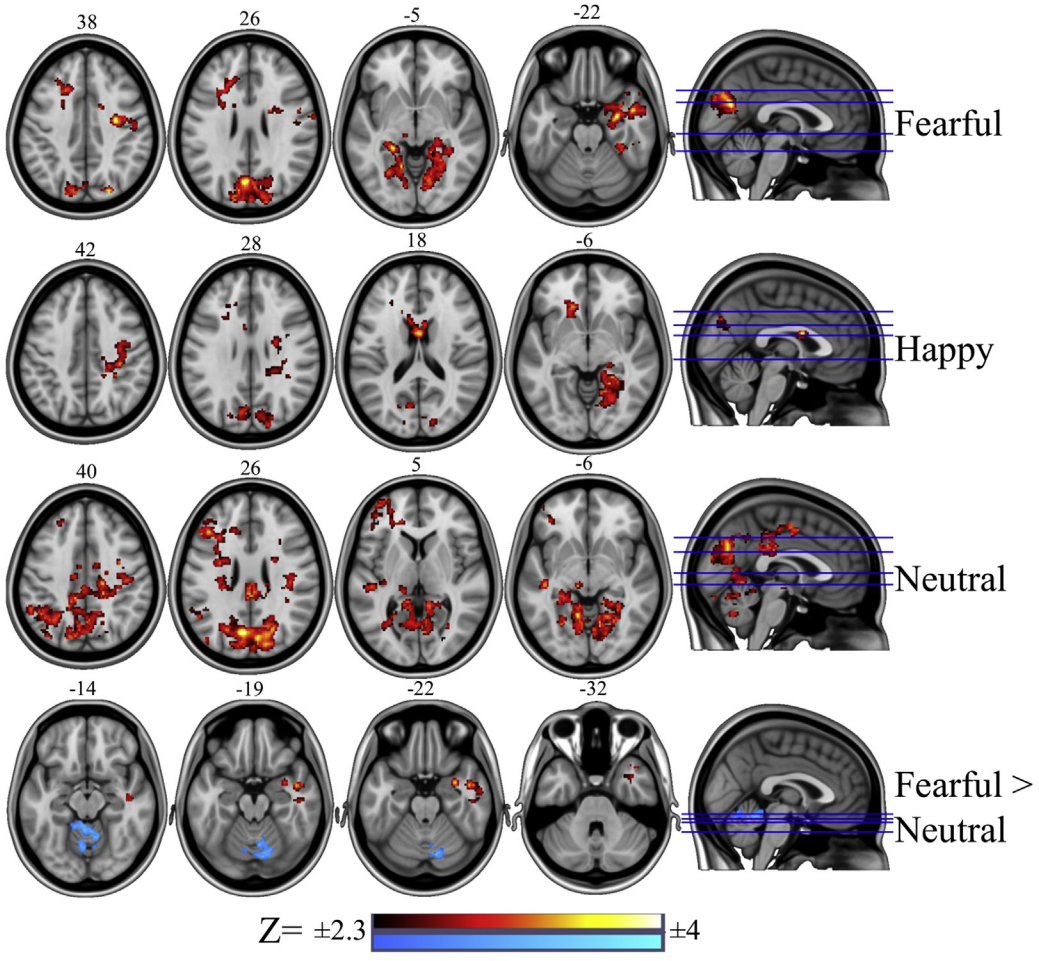


Fig. 3. Whole brain voxelwise changes. Significant clusters that showed increased (hot colours) or decreased (cool colours) responsivity after therapy (cluster corrected, $z > 2.3$, $p < .05$).

happy and neutral contrasts, in addition to increased BOLD responses in the amygdala, there were also increased responses in other visual areas. Whole brain increases for fearful > neutral were more limited to right amygdala and right middle temporal gyrus however.

3.3. Relationship with clinical outcomes

The *a priori* defined primary imaging outcome of interest was altered amygdala responses for fearful > neutral faces for after vs before therapy. We hypothesized that the increased amygdala

responsiveness was related to: 1) changes in *state* depression, measured via in-scanner ratings of depressed mood, and 2) changes in *trait* depression, measured via BDI scores at baseline and 1-week after therapy. Other exploratory relationships are shown in Table 1.

3.3.1. In-scanner ratings

State depression (0–20) was rated by patients directly after their 8-min faces scan. One day after psilocybin, 15 of 19 TRD patients (79%) showed a clinically meaningful response (in-scanner rating; reduction from baseline $\geq$ 50%) and treatment-response was significantly related to increased amygdala responses to fearful > neutral faces, with greater activations relating to better outcomes (Table 1). Response rates in state anxiety (42.1%) did not relate to changes in amygdala.

3.3.2. BDI

Change (10.2 ± 5.3), response (63.2%) and remission (57.9%) in BDI scores at 1-week were significantly related to post-treatment increases in amygdala responses to fearful > neutral faces, with greater activations relating to better outcomes (Table 1).

3.3.3. QIDS

Response at 1-day (68.4%), 1-week (63.2%) and 3-weeks (63.2%) were related to post-treatment increases in amygdala responses for fearful > neutral faces, again, with greater activations relating to better outcomes (Table 1). Response rates at 2-week (57.9%) and 5-week (47.3%) did not relate to changes in amygdala response.

Furthermore, it can be observed that responders and remitters had increased amygdala reactivity, while non-responders and non-remitters had decreased amygdala reactivity to fearful > neutral.

3.3.4. Effect of relapse?

Thirteen subjects were responders 1-day after therapy and 9 maintained response 5 weeks after therapy. Therefore, we looked at the difference in the amygdala response between the 4 'relapsed' and the 9 non-relapsed subjects at 5 week and found no differences in amygdala activation between these sub groups.

4. Discussion

Increased amygdala responses to emotional faces were observed one day after treatment with psilocybin for treatment-resistant depression. Post-treatment increases in amygdala responses to fearful versus neutral faces were related to a successful clinical outcome one week later.

Importantly, the present findings are in contrast to observations of decreased amygdala responses after treatment with conventional antidepressants and particularly with SSRIs (Ma, 2015). It has been proposed that decreased amygdala responsiveness to negative emotional stimuli under SSRIs is a key component of their therapeutic action (Harmer et al., 2017), but the present study's findings suggest that this model does not extend to the therapeutic action of psilocybin for TRD (Carhart-Harris and Nutt, 2017).

Observations of reduced amygdala responses to negative emotional stimuli (Ma, 2015) and reduced behavioural response biases to negative stimuli with conventional antidepressants (Harmer et al., 2009) have been interpreted as evidence of a functional remediation, linked to the correcting of negative cognitive biases in depression. However, it is suggested that chronically-used antidepressants have a more generalised effect on emotional processing, moderating not just responsiveness to negative emotional stimuli, but emotional stimuli more broadly (Price et al., 2009). Focusing specifically on the amygdala, this structure is known to be generally sensitive to emotional *salience*, regardless of the emotional valence of the stimuli (Adolphs, 2010; Santos et al.,

Table 1
Relationship between BOLD changes (after > before therapy; fearful > neutral) within the right amygdala and clinical outcomes. To avoid multiple comparisons, we hypothesized that amygdala changes would be related to two main clinical outcomes BDI at 1 week and in-scanner depression ratings. Other comparisons should be considered exploratory (QIDS, STAI and in-scanner state anxiety). The "Type of score" column describes how the test was done: Remission (BDI≤9) and Response (>50% reduction) were used to split the group for remitters/non-remitters or responders/non-responders. The differences between responders and non-responders and remitters and non-remitters are presented in the Max column which describe the z score in the Max voxel of difference, and the z scores of these categories separately are also reported in separate columns for the same voxel as in Max. The "Type of score" "Change" is the difference in the rating for After-Before. The "Change" in BDI and the change in amygdala response were entered to a GLM. Note that clusters close to MNI_152 coordinates (x,y,z) of 18,0,-20 are reliable as they survived cluster correction for few of the clinical outcomes. Furthermore, note that the significant clusters had reduced response for non-responders and non-remitters and enhanced response for responders and remitters. Real cluster sizes may be larger as the clusters in this table are constrained by the amygdala mask. N = 19.

Rating	Time point	Type of score	Volume (mm3)	Difference Max (z)	Non-resposnders or non-remitters (z)	Responders or Remitters (z)	MNI_152 Coordinates			Significance
							x	y	z	
In-scanner depression	1 day	Response (n = 10)	24	2.47	−2.18	1.5	18	0	−18	*
BDI	1 week	Remission (n = 11)	160	3.3	−2.25	2.42	22	0	−22	**
		Response (n = 12)	144	2.98	−2.48	1.86	18	0	−22	**
		Change (10.2 ± 5.3)	56	3	–	–	18	0	−20	*
QIDS	1 day	Response (n = 13)	192	3	−2.5	1.75	18	0	−20	**
	1 week	Response (n = 12)	104	2.9	−2.34	1.83	18	0	−20	*
	2 weeks	Response (n = 11)	–	–	–	–	–	–	–	–
	3 weeks	Response (n = 12)	104	2.9	−2.34	1.83	18	0	−20	*
	5 weeks	Response (n = 9)	–	–	–	–	–	–	–	–
In-Scanner anxiety	1 day	Response (n = 8)	–	–	–	–	–	–	–	–
STAI	1 week	Response (n = 6)	–	–	–	–	–	–	–	–
		Change (23.8 ± 15.2)	–	–	–	–	–	–	–	–

* z>2.3.
** z>2.3 (cluster corrected, p<0.05).

2011). It is possible that the notion that SSRIs have a *selective* action on amygdala responses to *negative* stimuli is fallible, and rather, SSRIs and related antidepressants have a more generalised muting influence on amygdala responses to emotionally *salient* stimuli. Relatedly, negative stimuli may be processed as especially salient, and thus be associated with greater amygdala responses – which are subsequently hyper-sensitive to intervention-led change.

Reduced amygdala responses to emotional stimuli after chronic antidepressant medication has been linked with activation of post-synaptic serotonin 1A receptors (5-HT1ARs), which have an inhibitory action on pyramidal cell firing (Andrade, 2011) and are densely expressed in the amygdala. While this mechanism has a solid empirical basis (Cowen and Browning, 2015; Deakin and Graeff, 1991), there is no known mechanism to explain how 5-HT1AR-induced attenuation of amygdala responsiveness can selectively apply to negative stimuli, without simultaneously affecting the processing of positive stimuli of an equivalent salience. Indeed, there is evidence of blunting of positive mood with SSRIs (Price et al., 2009). Moreover the relative ineffectiveness of conventional serotonergic antidepressant medications to alleviate anhedonia may be explained by a generalised moderation of emotional responsiveness with these drugs (McCabe et al., 2010).

We recently carried out a qualitative analysis of patient experiences from this clinical trial, asking patients whether psilocybin with psychological support has been effective for them, and if so, how? Since the majority of patients reported improvements with the treatment, most answered in the affirmative and described a greater willingness to *accept all emotions* post-treatment (including negative ones). These effects were often contrasted with those of their previous depression treatments which they described as working to reinforce emotional avoidance and disconnection (Watts et al., 2017). Conversely, psilocybin was said to make emotional 'confrontation' more likely, and the accompanying psychological support helped patients achieve an emotional breakthrough (catharsis) and resolution (Eisner and Cohen, 1958; Gasser et al., 2014b). Consistently, recent work has suggested that overcoming challenging emotional phenomena under a psychedelic is predictive of better long-term mental health outcomes (Carbonaro et al., 2016).

It is important to highlight an important discrepancy between the present results, observed post acutely in patients treated with psilocybin for major depression viewing emotional faces and those from a previous study in which amygdala responses to emotional stimuli (not faces) were assessed during the acute psilocybin 'high' in healthy individuals (Kraehenmann et al., 2015). This latter study reported unspecific decreases in right amygdala responses to negative and neutral stimuli under psilocybin, which, based on the aforementioned similarities with the action of conventional antidepressants, the authors interpreted as supporting an antidepressant action for psilocybin. We advise caution with this interpretation however, not least because our pre versus post resting-state fMRI findings suggest that post-acute changes in spontaneous brain function are very different if not antithetical to psilocybin's acute brain effects (Carhart-Harris et al., 2017). Moreover, findings of 'attenuated responses' with potent interventions may be explained by compromised task engagement. A consistent explanation has been used to account for apparent functional impairments in imaging studies of pathological states such as schizophrenia, i.e. impoverished responses are observed because patients do not properly engage with the task and its stimuli (Corbetta et al., 1990; Rees et al., 1997).

It is important to acknowledge the limitations of the present study. It would be interesting to collect longer-term imaging data than the 1-day post treatment scanning point chosen here (e.g. one week and one month after treatment with psilocybin). If feasible, it would also be interesting to collect imaging data *during* the acute experience to see how this relates to post treatment brain changes. Future work may look to combine PET and fMRI to systematically address potential relationships between receptor densities and functional brain measures before and after treatment with psilocybin. The recruitment of a healthy control group, receiving the same interventions would also add value, as would the inclusion of a meaningful comparator condition such as psilocybin alone versus psilocybin in combination with psychological support, plus the same for placebo and perhaps an active pharmacological control, such as an SSRI and/or methylphenidate (Griffiths et al., 2006). As this study was not placebo controlled, the contribution of psilocybin with psychological support cannot be differentiated from psychological support and other aspects of the therapy. It would also be worthwhile to see if the present results extend to a less severe population of depressed patients, including those with less extensive histories of exposure to psychiatric medication.

Psilocybin represents a novel intervention for major depression that appears to be safe, rapid and potentially enduring in its antidepressant action. Furthermore, it is important to note that psilocybin's abuse potential is low (Johnson and Griffiths, 2017). The original rationale for using psychedelic ('mind-revealing') drugs as aides to psychotherapy was that they serve to dismantle psychological defences, allowing suppressed emotional material to surface, sometimes with cathartic effect (Eisner and Cohen, 1958; Gasser et al., 2014b; Grof et al., 2008). The present findings of increased amygdala responsiveness post psilocybin resonate with patients' descriptions of feeling emotionally re-connected and accepting after the treatment (Watts et al., 2017). The finding of a relationship between increased right amygdala responses to fearful > neutral faces post treatment and subsequent clinical improvements adds further endorsement to this interpretation. Future work is required to test the replicability of these findings and test whether enhanced amygdala responsiveness is related to the potentially enduring positive mood effects of psychedelics (Griffiths et al., 2006; Schmid and Liechti, 2017). If confirmed, this would suggest an alternative neurobiological basis to the alleviation of depressive symptoms distinct from that of the SSRI antidepressants (Carhart-Harris and Nutt, 2017).

> *""I felt so much lighter, like something had been released, it was an emotional purging, the weight and anxiety and depression had been lifted."*
>
> *""I have felt a sense of acceptance; more acceptance of agony, boredom, loneliness. [A] willingness to try to accept the negative times - but also an appreciation of the wonderful times."*
>
> (Two patients' testimonies from recent psilocybin for TRD trial) (Carhart-Harris et al., 2016; Watts et al., 2017).

Funding and disclosure

The authors declare no conflict of interest. LR is funded by the Imperial College Scholarship Scheme. LD and MBW are funded by Imanova, DJN is funded by the Edmund J Safra Foundation (P17264) and RLC-H is funded by the Alex Mosely Charitable Trust (G30444).

Acknowledgments

This work was supported by an MRC clinical development scheme grant (MR/J00460X/1), the Alex Mosley Charitable Trust and by the COMPASS group (I30006). This work was carried out as part of the Beckley/Imperial Research Collaboration.

References

Adolphs, R., 2010. What does the amygdala contribute to social cognition? Ann. N. Y.

Acad. Sci. 1191, 42–61.
Andrade, R., 2011. Serotonergic regulation of neuronal excitability in the prefrontal cortex. Neuropharmacology 61, 382–386.
Avants, B.B., Tustison, N., Song, G., 2009. Advanced normalization tools (ANTS). Insight J 2, 1–35.
Beck, A.T., Steer, R.A., Carbin, M.G., 1988. Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. Clin. Psychol. Rev. 8, 77–100.
Bogenschutz, M.P., Johnson, M.W., 2016. Classic hallucinogens in the treatment of addictions. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 64, 250–258.
Carbonaro, T.M., Bradstreet, M.P., Barrett, F.S., MacLean, K.A., Jesse, R., Johnson, M.W., Griffiths, R.R., 2016. Survey study of challenging experiences after ingesting psilocybin mushrooms: acute and enduring positive and negative consequences. J. Psychopharmacol., 0269881116662634
Carhart-Harris, R.L., Bolstridge, M., Rucker, J., Day, C.M., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J.A., Forbes, B., Feilding, A., 2016. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. The Lancet Psychiatry 3 (7), 619–627.
Carhart-Harris, R.L., Nutt, D.J., 2017. Serotonin and brain function: a tale of two receptors. J. Psychopharmacol. 31 (9), 1091–1120.
Carhart-Harris, R.L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, N., Wall, M., Tanner, M., Kaelen, M., Murphy, K., Leech, R., Curran, H.V., Nutt, D.J., 2017. Psilocybin for Treatment-resistant Depression: FMRI-measured Brain Mechanisms. Sci. Rep. 7 (1), 13187.
Corbetta, M., Miezin, F.M., Dobmeyer, S., Shulman, G.L., Petersen, S.E., 1990. Attentional modulation of neural processing of shape, color, and velocity in humans. Science 248, 1556.
Cowen, P.J., Browning, M., 2015. What has serotonin to do with depression? World Psychiatr. 14, 158–160.
Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.
Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis: I. Segmentation and surface reconstruction. Neuroimage 9, 179–194.
Deakin, J.W., Graeff, F.G., 1991. 5-HT and mechanisms of defence. J. Psychopharmacol. 5, 305–315.
dos Santos, R.G., Osório, F.L., Crippa, J.A.S., Riba, J., Zuardi, A.W., Hallak, J.E., 2016. Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): a systematic review of clinical trials published in the last 25 years. Therapeutic Advances in Psychopharmacology, 2045125316638008.
Drevets, W.C., Videen, T.O., Price, J.L., Preskorn, S.H., Carmichael, S.T., Raichle, M.E., 1992. A functional anatomical study of unipolar depression. J. Neurosci. 12, 3628–3641.
Eisner, B.G., Cohen, S., 1958. Psychotherapy with lysergic acid diethylamide. J. Nerv. Ment. Dis. 127, 528–539.
Gasser, P., Holstein, D., Michel, Y., Doblin, R., Berra Yazar-Klosinski, P., Passie, T., Brenneisen, R., 2014a. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J. Nerv. Ment. Dis. 202 (7), 513.
Gasser, P., Kirchner, K., Passie, T., 2014b. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. J. Psychopharmacol., 0269881114555249
Godlewska, B., Norbury, R., Selvaraj, S., Cowen, P., Harmer, C., 2012. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. Psychol. Med. 42, 2609–2617.
Goeleven, E., De Raedt, R., Leyman, L., Verschuere, B., 2008. The Karolinska directed emotional faces: a validation study. Cognit. Emot. 22, 1094–1118.
Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P., Klinedinst, M.A., 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J. Psychopharmacol. 30, 1181–1197.
Griffiths, R.R., Johnson, M.W., Richards, W.A., Richards, B.D., McCann, U., Jesse, R., 2011. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology 218, 649–665.
Griffiths, R.R., Richards, W.A., McCann, U., Jesse, R., 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology 187, 268–283.
Grinspoon, L., Bakalar, J.B., 1979. Psychedelic Drugs Reconsidered. Basic Books, New York.
Grob, C.S., Danforth, A.L., Chopra, G.S., Hagerty, M., McKay, C.R., Halberstadt, A.L., Greer, G.R., 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch. Gen. Psychiatr. 68, 71–78.
Grof, S., Hofmann, A., Weil, A., 2008. LSD Psychotherapy (The Healing Potential of Psychedelic Medicine). Multidisciplinary Association for Psychedelic Studies, Ben Lomond, CA.
Harmer, C.J., Duman, R.S., Cowen, P.J., 2017. How do antidepressants work? New perspectives for refining future treatment approaches. The Lancet Psychiatry 195 (2), 102–108.
Harmer, C.J., Goodwin, G.M., Cowen, P.J., 2009. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br. J. Psychiatr. 195, 102–108.
Hofmann, A., Heim, R., Brack, A., Kobel, H., 1958. Psilocybin, ein psychotroper Wirkstoff aus dem mexikanischen RauschpilzPsilocybe mexicana Heim. Cell. Mol. Life Sci. 14, 107–109.
Jack, C.R., Bernstein, M.A., Fox, N.C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P.J., L Whitwell, J., Ward, C., 2008. The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. J. Magn. Reson. Imag. 27, 685–691.
Janak, P.H., Tye, K.M., 2015. From circuits to behaviour in the amygdala. Nature 517, 284–292.
Johnson, M.W., Griffiths, R.R., 2017. The Abuse Potential of Medicinal Psilocybin According the 8 Factors of the United States Controlled Substances Act.
Kraehenmann, R., Preller, K.H., Scheidegger, M., Pokorny, T., Bosch, O.G., Seifritz, E., Vollenweider, F.X., 2015. Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. Biol. Psychiatr. 78, 572–581.
Ma, Y., 2015. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. Mol. Psychiatr. 20, 311–319.
Majić, T., Schmidt, T.T., Gallinat, J., 2015. Peak experiences and the afterglow phenomenon: when and how do therapeutic effects of hallucinogens depend on psychedelic experiences? J. Psychopharmacol. 29, 241–253.
McCabe, C., Mishor, Z., Cowen, P.J., Harmer, C.J., 2010. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. Biol. Psychiatr. 67, 439–445.
Mithoefer, M.C., Grob, C.S., Brewerton, T.D., 2016. Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. The Lancet Psychiatry 3, 481–488.
Moreno, F.A., Wiegand, C.B., Taitano, E.K., Delgado, P.L., 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J. Clin. Psychiatr. 67, 1735–1740.
Osório, F. d. L., Sanches, R.F., Macedo, L.R., dos Santos, R.G., Maia-de-Oliveira, J.P., Wichert-Ana, L., de Araujo, D.B., Riba, J., Crippa, J.A., Hallak, J.E., 2015. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. Rev. Bras. Psiquiatr. 37, 13–20.
Pahnke, W.N., Kurland, A.A., Unger, S., Savage, C., Grof, S., 1970. The experimental use of psychedelic (LSD) psychotherapy. Jama 212, 1856–1863.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154.
Price, J., Cole, V., Goodwin, G.M., 2009. Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study. Br. J. Psychiatr. 195, 211–217.
Rees, G., Frith, C.D., Lavie, N., 1997. Modulating irrelevant motion perception by varying attentional load in an unrelated task. Science 278, 1616–1619.
Riedel, M., Möller, H.-J., Obermeier, M., Schennach-Wolff, R., Bauer, M., Adli, M., Kronmüller, K., Nickel, T., Brieger, P., Laux, G., 2010. Response and remission criteria in major depression–a validation of current practice. J. Psychiatr. Res. 44, 1063–1068.
Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S.E., Belser, A., Kalliontzi, K., Babb, J., 2016. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J. Psychopharmacol. 30, 1165–1180.
Rucker, J.J., Jelen, L.A., Flynn, S., Frowde, K.D., Young, A.H., 2016. Psychedelics in the treatment of unipolar mood disorders: a systematic review. J. Psychopharmacol. 30, 1220–1229.
Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., 2003. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatr. 54, 573–583.
Santos, A., Mier, D., Kirsch, P., Meyer-Lindenberg, A., 2011. Evidence for a general face salience signal in human amygdala. Neuroimage 54, 3111–3116.
Schmid, Y., Liechti, M.E., 2017. Long-lasting subjective effects of LSD in normal subjects. Psychopharmacology 1–11.
Sergerie, K., Chochol, C., Armony, J.L., 2008. The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. Neurosci. Biobehav. Rev. 32, 811–830.
Siegel, J.S., Power, J.D., Dubis, J.W., Vogel, A.C., Church, J.A., Schlaggar, B.L., Petersen, S.E., 2014. Statistical improvements in functional magnetic resonance imaging analyses produced by censoring high-motion data points. Hum. Brain Mapp. 35, 1981–1996.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23, S208–S219.
Spain, A., Howarth, C., Khrapitchev, A.A., Sharp, T., Sibson, N.R., Martin, C., 2015. Neurovascular and neuroimaging effects of the hallucinogenic serotonin receptor agonist psilocin in the rat brain. Neuropharmacology 99, 210–220.
Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., 1970. STAI Manual for the Stait-trait Anxiety Inventory (" Self-evaluation Questionnaire"). Consulting Psychologists Press Palo Alto, Calif.
Watts, R., Day, C., Krzanowski, J., Nutt, D., Carhart-Harris, R., 2017. Patients' accounts of increased “connectedness” and “acceptance” after psilocybin for treatment-resistant depression. J. Humanist. Psychol., 0022167817709585