

1 **Increased low-frequency brain responses to music after psilocybin therapy**
2 **for depression**

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27

28 **Abstract**

29 Psychedelic-assisted psychotherapy with psilocybin is an emerging therapy with great
30 promise for depression, and modern psychedelic therapy (PT) methods incorporate music as a
31 key element. Music is an effective emotional/hedonic stimulus that could also be useful in
32 assessing changes in emotional responsiveness following psychedelic therapy. Brain
33 responses to music were assessed before and after PT using functional Magnetic Resonance
34 Imaging (fMRI) and ALFF (Amplitude of Low Frequency Fluctuations) analysis methods.
35 Nineteen patients with treatment-resistant depression underwent two treatment sessions
36 involving administration of psilocybin, with MRI data acquired one week prior and the day
37 after completion of the second of two psilocybin dosing sessions. Comparison of music-
38 listening and resting-state scans revealed significantly greater ALFF in bilateral superior
39 temporal cortex for the post-treatment music scan, and in the right ventral occipital lobe for
40 the post-treatment resting-state scan. ROI analyses of these clusters revealed a significant
41 effect of treatment in the superior temporal lobe for the music scan only. Somewhat
42 consistently, voxelwise comparison of treatment effects showed relative increases for the
43 music scan in the bilateral superior temporal lobes and supramarginal gyrus, and relative
44 decreases in the medial frontal lobes for the resting-state scan. ALFF in these music-related
45 clusters was significantly correlated with intensity of subjective effects felt during the dosing
46 sessions. These data suggest a specific effect of PT on the brain's response to a hedonic
47 stimulus (music), implying an elevated responsiveness to music after psilocybin therapy that
48 was related to subjective drug effects felt during dosing.

49 **Introduction**

50 The use of psychotropic compounds for medicinal, spiritual, and recreational purposes has
51 ancient origins in a diverse set of human cultures, and likely stretches back into pre-history
52 (Hardy, 2021). A recent revival of interest in the clinical potential of these compounds has
53 found that classic psychedelics such as psilocybin may have utility in the treatment of
54 depression (Carhart-Harris et al., 2021; Carhart-Harris et al., 2016), addiction (Johnson,
55 Garcia-Romeu, Cosimano, & Griffiths, 2014), and anxiety (Grob et al., 2011). Modern
56 neuroscientific research is beginning to understand the potential physiological and
57 psychopharmacological mechanisms behind these therapeutic effects (Carhart-Harris et al.,
58 2017; Mertens et al., 2020).

59 Music is also pervasively, and perhaps universally, enjoyed across cultures and throughout
60 human history (Cross, 2001), and has deep biological and evolutionary foundations (Fitch,
61 2006). The use of music in a therapeutic context dates back to at least Pythagoras (Nilsson,
62 2008) and also features in the ancient Indian medical system of Ayurveda (Sundar, 2007).
63 Modern research has started to identify the neurological underpinnings of the unique role that
64 music plays in human cultural and emotional life (Reybrouck, Vuust, & Brattico, 2018) and
65 its potential clinical use (Bower, Magee, Catroppa, & Baker, 2021; Nilsson, 2008). The
66 brain's reward system, which includes the ventral striatum and ventro-medial pre-frontal
67 cortex (vmPFC), appears to be implicated in pleasurable emotional responses to music
68 (Koelsch, 2020). The primary auditory cortex (superior temporal gyrus, Heschl's gyrus) is
69 another relevant system for music perception (Koelsch, Skouras, & Lohmann, 2018) and
70 limbic brain regions have also been implicated in emotional responses to music (Koelsch &
71 Skouras, 2014). Music can evoke a range of emotions but generally can be considered a
72 hedonic stimulus, capable of evoking positively valenced emotions. It is therefore a
73 potentially useful tool for indexing anhedonia, i.e. the relative inability to experience
74 pleasure; a common symptom of depression (Cao et al., 2019). Previous studies have shown
75 decreased responses to music in the neural reward system in depressed patients (Jenkins et
76 al., 2018; Osuch et al., 2009).

77 Recent research on the effect of psychotropic drugs on music perception has shown that
78 classic psychedelics, like LSD, can enhance the subjective emotional response to music
79 (Kaelen et al., 2015), and that brain responses to music are also significantly increased
80 (Kaelen et al., 2017). The hippocampus has been identified as a key region involved in both

81 the effects of LSD and music, alone, and in combination (Kaelen et al., 2016). Music plays a
82 central role in modern and historic versions of psychedelic therapy, useful both for its
83 calming effects at various stages of the therapeutic process, and for its ability to act
84 synergistically with the drug to guide and potentially enhance emotional experiences and
85 evoke autobiographical memories (Barrett, Preller, & Kaelen, 2018; Kaelen et al., 2016).

86 The aim of the present study was to examine the effects of psychedelic therapy for depression
87 on the brain's response to music using functional Magnetic Resonance Imaging (fMRI),
88 comparing a music-listening scan to a resting-state scan, before and after treatment. To do so,
89 we used a measure of the brain's Low-Frequency Oscillations (LFOs) known as ALFF
90 (Amplitude of Low-Frequency Fluctuations; Zang et al., 2007). ALFF is a spatially
91 unconstrained analysis method that is well-suited for characterizing both resting-state and
92 stimulus-related brain activity and has high test-retest reliability (Li, Kadivar, Pluta, Dunlop,
93 & Wang, 2012). We also investigated the relationship between the derived ALFF results and
94 subjective clinical/psychometric results obtained during and after the therapy sessions.

95 **Methods**

96 This study was approved by the National Research Ethics Service (NRES) committee (West
97 London) and was conducted in accordance with the revised declaration of Helsinki (2000),
98 Good Clinical Practice (GCP) guidelines, and the National Health Service (NHS) Research
99 Governance Framework. Imperial College London sponsored the research which was
100 conducted under a Home Office license for research with schedule 1 drugs, and the
101 Medicines and Healthcare products Regulatory Agency (MHRA) also approved the study.
102 All patients gave written informed consent. The study used facilities at the Imperial College
103 Clinical Research Facility, and Invicro London.

104 The resting-state data used in this work has been previously analysed and reported (Carhart-
105 Harris et al., 2017) but not using an ALFF analysis. The presently reported results therefore
106 derive from a novel analysis of the resting-state data, combined with the music-listening data
107 from the same subjects. The music-listening fMRI data has not been previously reported.

108 *Participants and Recruitment*

109 Nineteen subjects were recruited and completed the study, including thirteen males and six
110 females, aged between 27-64. The mean age of participants was 41.3 (SD=10.5), and all had
111 diagnoses of treatment resistant major depression. Initial screening included physical health
112 assessments (electrocardiogram, blood and urine tests), a psychiatric interview, an assessment
113 by a qualified clinician, and self-report questionnaires. The key inclusion criteria were a
114 diagnosis of moderate to severe depression, with a score of 17 or higher on the 21-item
115 Hamilton Depression Rating Scale (HAM-D), and treatment-resistance, meaning that they
116 had been non-responsive to at least two previous pharmacological treatments. Exclusion
117 criteria included previous or current psychotic disorders, individuals with a history of
118 psychotic disorders in their immediate family members, previous suicide attempts that led to
119 hospitalization, pregnancy, drug or alcohol dependence, phobia of blood or needles, history
120 of mania, other concurrent medications, and general contraindications for MRI scanning.

121 *Design and Procedure*

122 For full details of the study procedure please see the original report of the clinical data
123 (Carhart-Harris et al., 2016). The study was an open-label design with no control group or
124 placebo, and all subjects received the active intervention with full prior disclosure. The
125 psilocybin used in the study was obtained from THC-pharm (Frankfurt, Germany), and
126 processed into size 0 capsules with 5 mg psilocybin each, by Guy's and St Thomas'
127 Hospitals' Pharmacy Manufacturing Unit (London, UK).

128 Psilocybin was administered to the participants in two therapy sessions: low dose (10mg) in
129 the first session and high dose (25mg) in the second session one week later. Post capsule
130 ingestion, patients lay with eyes closed while listening to music. Two therapists were always
131 present, and adopted a non-directive, supportive approach for the duration of the sessions.

132 MRI scanning visits were conducted one week prior to the first therapy/dosing visit, and the
133 day after the second therapy/dosing session. The primary clinical outcome was the Quick
134 Inventory of Depressive Symptoms (Rush et al., 2003) and this was administered at baseline,
135 weekly from week one to week five, and finally at a three-month follow-up. Other
136 questionnaire measures included the 5D-ASC (5-dimension altered states of consciousness
137 questionnaire; administered 6-7 hours post-dosing, at each dosing session; Dittrich, 1998) and
138 the GEMS-3 (Geneva Emotional Music Scale; Zentner, Grandjean, & Scherer, 2008), which
139 was administered immediately after each MRI scanning session in order to assess the
140 subjective response to the music-listening scan. For full details of all questionnaire measures
141 see Carhart-Harris et al. (2016).

142

143 *Stimuli and Image Acquisition*

144 Subjects were instructed to keep their eyes closed for the duration of the resting-state and
145 music scans. A prompt with these instructions was displayed on the screen during the scan as
146 a reminder in case they opened their eyes at any point.

147 Music stimuli used in this study were edited compositions by Carlos Cipa. A different music
148 track was played on each scan visit, and the order of the playlist was randomized across
149 subjects. 'Lost and Delirious' and 'Lie with Me' were combined in the first track; and 'Wide

150 and Moving' and 'The Dream' were combined in the second track. All tracks used were solo
151 piano works, with no vocals or other instruments. The tracks were chosen in order to balance
152 emotional potency, based on ratings by an independent sample. Ableton Live 9 software was
153 used to boost the volume and apply audio compression in order to provide maximally-audible
154 stimuli that could be easily heard over the background noise of the scanner. Music was
155 played through MRI-compatible headphones (MR Confon) during the scan.

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

161 T2*-weighted echo-planar images (EPI) for BOLD contrast were acquired for the functional
162 scans (3 mm isotropic voxels, TR = 2000 ms, TE = 31 ms, 36 axial slices, 192 mm in-plane
163 FOV, flip angle = 80°, bandwidth = 2298 Hz/pixel, GRAPPA = 2). Both the resting and
164 music scans were 240 volumes or exactly eight minutes in duration. Data from other scan
165 sequences was also collected during each session, and these have been reported previously
166 elsewhere (Carhart-Harris et al., 2017; Mertens et al., 2020; Roseman, Demetriou, Wall,
167 Nutt, & Carhart-Harris, 2018).

168 *Data Analysis*

169 All analyses were performed using the FMRIB Software Library (FSL; v.6.03) and Analysis
170 of Functional NeuroImages (AFNI) software. Anatomical data were processed using the
171 `fsl_anat` script which involved skull-stripping and segmentation into White Matter (WM) and
172 Cerebrospinal Fluid (CSF) masks with FMRIB's Automated Segmentation Tool (FAST).
173 These anatomical masks were registered to each subject's functional space, and time-series
174 from the pre-processed (see below) functional data were extracted to be used for later
175 analysis.

176 Pre-processing of the functional data used FSL's FEAT module and included head-motion
177 correction, spatial smoothing with a 6mm Gaussian filter, pre-whitening and correction of
178 auto-correlation of the time-series with FSL's FILM algorithm, and registration to standard
179 (MNI152) space. FEAT analysis models included the CSF and WM time-series, and six
180 head-motion parameters (three translations, and three rotations) as regressors (Wolletz et al.,

181 2019). The purpose of these first-level analysis models was to de-noise the data by regressing
182 out these eight time-series, and all subsequent analyses therefore used the residuals images
183 produced by FEAT. These images were transformed into standard (MNI152) space using the
184 parameters also derived by FEAT. The ALFF analyses were then performed on each
185 individual subject's pre-processed, de-noised, standard-space data using the AFNI 3dRSFC
186 script. The data were band-pass filtered using a range of 0.01-0.1Hz in these analyses.

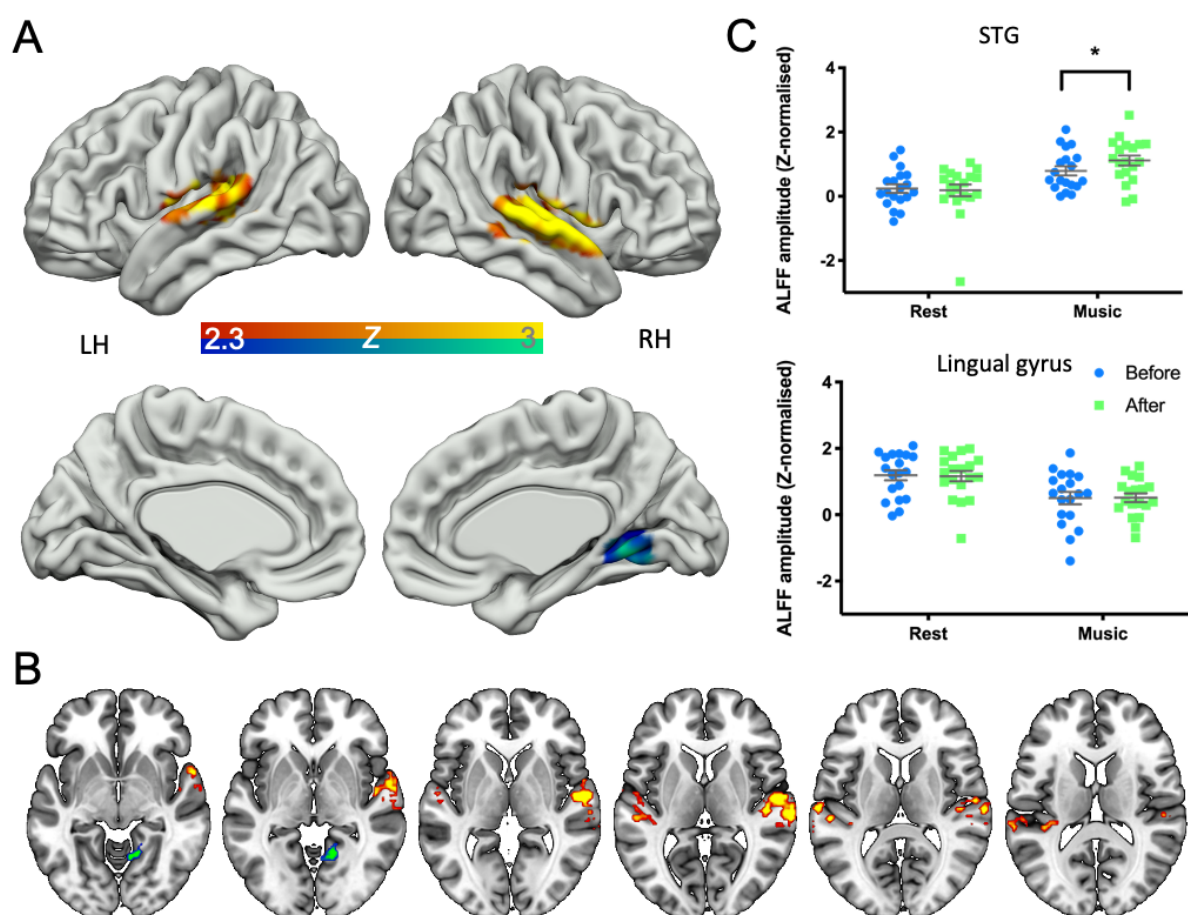
187 The resulting ALFF images were then combined in group-level analyses using FSL's
188 Ordinary Least Squares (OLS) mixed effects model. Results were thresholded at $Z = 2.3$, $p <$
189 0.05 (cluster-corrected for multiple comparisons). A single group mean average model (all
190 subjects, all scans) was used to observe the overall spatial distribution of LFOs and to
191 validate the methods. A separate group-level model was used to examine the main effect of
192 the task (i.e. the difference between all music-listening scans, and all resting-scans). Further
193 separate group-level models were used to compare the effect of the drug treatment/therapy
194 within each scan type (i.e. after vs. before therapy for the rest scans, and after vs. before
195 therapy for the music scans).

196 Following the recommendations of (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006) and
197 similar procedures used in (Yang et al., 2020) we defined functional Regions of Interest
198 (ROIs) for further investigation. The first set of ROIs was defined from clusters identified in
199 the main task effect analysis (music vs. resting scans). These were used to investigate the
200 effect of psilocybin therapy in the clusters which showed a significant task-dependent
201 difference. The second set of ROIs was defined from clusters resulting from the specific
202 comparisons of before vs. after psilocybin therapy, in each functional task scan. These were
203 used to assess relationships (using Pearson's correlations) with appropriate psychometric
204 measures: the 5D-ASC, the GEMS-3, and the QIDS questionnaires. All ROI data were Z-
205 normalised before further analysis.

206 Results

207 The mean (all subjects, all scans) analysis of the ALFF measure showed a regional
208 distribution of values similar to what is typically observed in ALFF studies (e.g. Zou et al.,
209 2008). High values were observed in ventral brain regions (likely attributable to physiological
210 noise) but also in the cingulate cortex, medial and lateral frontal lobes, and insula (see
211 supplementary figure S1).

212 Comparison of mean effects of scan type (all resting-state scans vs. all music-listening scans
213 contrasted but pre vs post treatment collapsed into one) showed relatively higher ALFF
214 values in the bilateral superior temporal gyrus (primary auditory cortex) for the music-
215 listening scan, and a relatively higher response in the lingual gyrus for the resting-state scan.



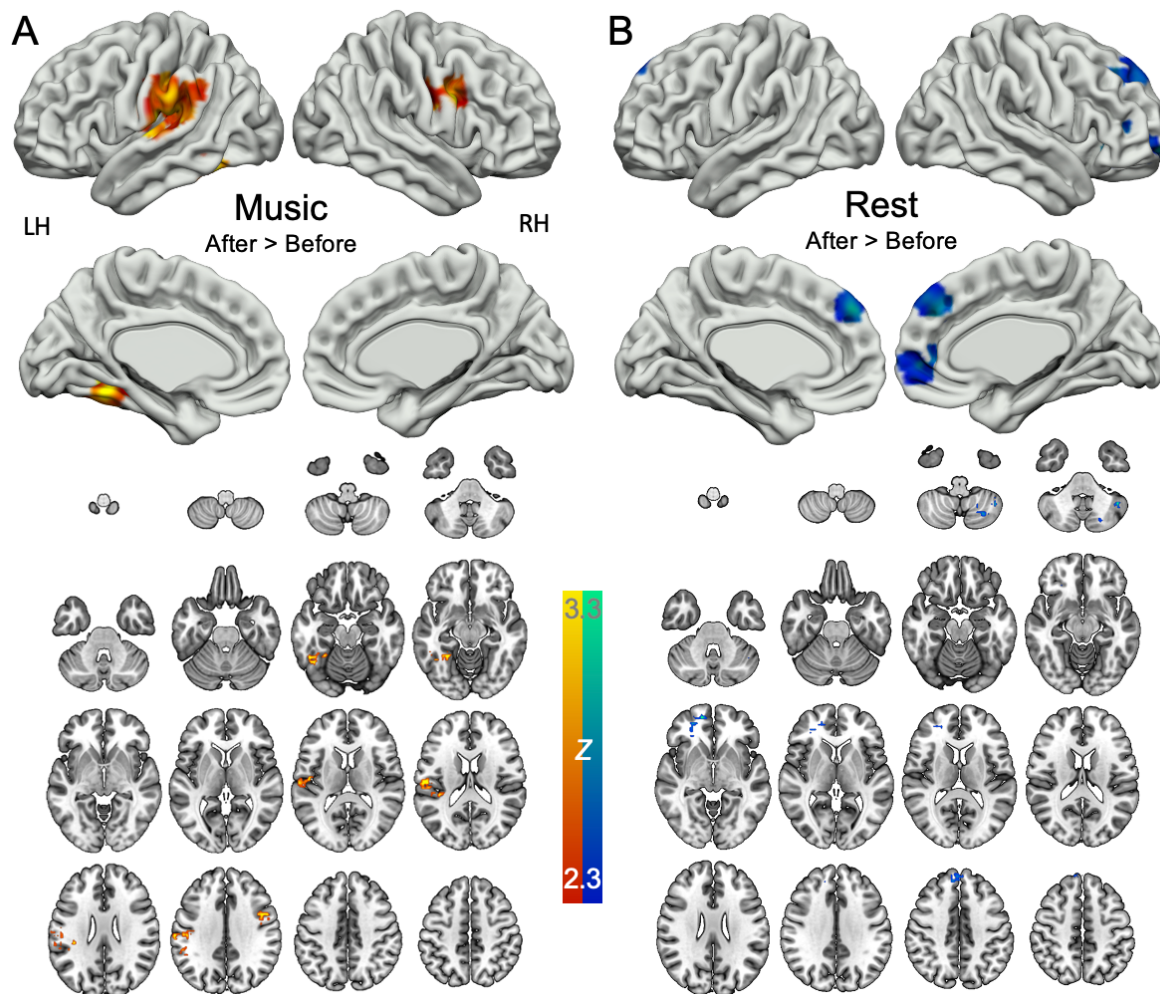
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217 Figure 1. A: Comparison of the two scan types (resting-state or 'rest' vs. music), with
218 pre and post treatment collapsed (panel A = 3D render, B = axial slices). The red-
219 yellow colour-scale denotes greater responses in the music-listening (vs rest), and the
220 blue-green colour-scale denotes greater responses in the resting scan (vs music). Panel

221 C: ROI data from the two task-defined ROIs. Significant effect of treatment in the
222 music/superior temporal gyrus (STG) ROI, for the music scan ($p=0.045$). Clear main
223 effects of scan type (rest vs. music) are also evident here in both regions because
224 these ROIs were selected on that basis.

225 These two regions were defined as ROIs and the effects of treatment (before vs. after
226 psychedelic therapy) and scan type (rest vs. music) were examined using 2x2 ANOVA
227 models. For the lingual gyrus region, there was only a main effect of scan type ($F[1,18] =$
228 $38.45, p < 0.001$), which is expected as the ROIs were selected on the basis of differential
229 response to the two scans. In the superior temporal gyrus region, there was likewise a scan
230 type main effect ($F[1,18] = 32.89, p < 0.001$) but also a significant interaction with treatment
231 ($F[1,18] = 4.90, p = 0.04$). Post-hoc tests revealed the source of this interaction to be a
232 significant increase in responses in this region *after* psilocybin therapy, but only for the
233 music-listening scan ($t[31] = 2.09, p = 0.045$). See histograms on figure 1. This suggests a
234 specific effect of increased LFOs in the superior temporal lobe after the therapy when
235 listening to music. There was no effect of the therapy on the resting state scan in this superior
236 temporal lobe region, and no effects of the therapy in the lingual gyrus region (in either scan
237 type). Additional analyses examined potential differences between the two music tracks and
238 the effectiveness of the counterbalancing. An additional between-subjects factor of track
239 order was also included (i.e., subjects who received track A on visit 1, vs. subjects who
240 received track B on visit 1). These analyses showed no main effects of track order and no
241 significant interactions with the other factors (all p values > 0.1) in either of the ROIs.

242 Voxelwise comparisons of the resting-state data before vs. after treatment within each scan
243 type (figure 2) showed an effect in the medial frontal lobe (before $>$ after), suggesting
244 decreased ALFF in these regions after the therapy. We also see relative increases in ALFF
245 (after $>$ before) in the music scan, in a lateral region covering the superior temporal areas and
246 the supramarginal gyrus in the left hemisphere, and a similar, though somewhat smaller and
247 more anterior region in the right hemisphere, centred on the inferior portion of the precentral
248 gyrus. An additional small cluster in the left lingual gyrus is also present in this comparison.

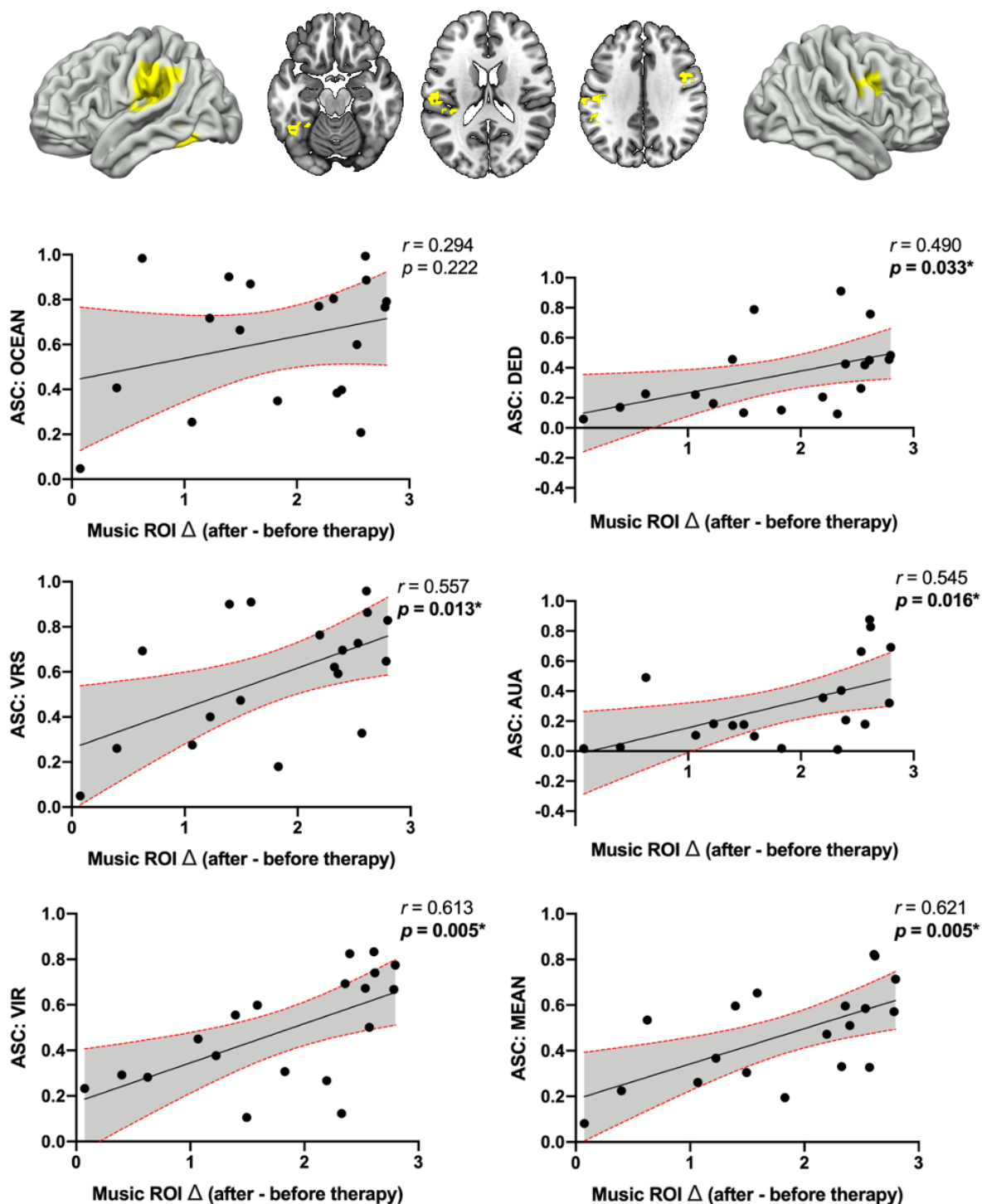


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250 Figure 2. Comparison of pre- and post-therapy effects (after > before) for each scan
251 individually (A = music; B = resting). The red-yellow colour-scale denotes increased
252 responses post-therapy and the blue-green colour-scale denotes decreased responses
253 post-therapy. ALFF values during the music scan were higher post-therapy with
254 significant clusters observed in the supramarginal gyrus, extending down into the
255 superior temporal lobe (left hemisphere), the inferior portion of the pre-central gyrus
256 (right hemisphere), and a small cluster in the left lingual gyrus. In the resting-state
257 scan, ALFF values were reduced post-therapy in the medial frontal lobe.

258 These activation clusters were also defined as ROIs and the delta (change in response
259 between pre- and post-therapy scans: after minus before) was calculated on data from these
260 ROIs. Performing correlations on these measures with clinical and psychometric scores
261 showed that the change in response to music in the post-therapy scan was significantly
262 correlated with several sub-scales of the ASC scale acquired on the second (high-dose)
263 treatment visit (figure 3). The DED (ego-dissolution), VRS (visionary restructuralization),

264 AUA (auditory alterations) and VIR (vigilance reduction) sub-scales showed significant
265 relationships, while the OCEAN (oceanic boundlessness) sub-scale was non-significant. The
266 mean of all five sub-scales was also highly correlated with the ROI data ($r = 0.621, p =$
267 0.005). The mean of all sub-scales and the result from the VIR sub-scale ($r = 0.613, p =$
268 0.005) survive family-wise correction for multiple comparisons with a corrected alpha level
269 of $p = 0.008$. There were no other relationships between the music scan data and any other
270 subjective questionnaire measure or clinical rating scale, and similar analyses with the rest
271 scan data also showed no significant relationships with any of the questionnaire measures.
272 See the supplementary material for full tables of correlation results.



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Figure 3. Exploratory correlational analyses between increased ALFF during music after therapy vs before (ROI: top row) and the five-dimensional altered states of consciousness sub-scales. OCEAN = “Oceanic boundlessness”; DED = “Ego-dissolution”; VRS = “Visionary restructuring”; AUA = “Auditory alterations”; VIR = “Vigilance reduction”. MEAN = Mean of all five sub-scales (also known as the ‘global’ ASC score). Significant correlations ($p < 0.05$) are highlighted with bold

280 text and *. The VIR and mean/global scores (bottom two panels) survive a family-
281 wise corrected p value threshold of 0.008.

282 Discussion

283 ALFF identified brain regions in the superior temporal lobe in which low-frequency
284 fluctuations were greater during music listening compared with (no-music) resting-state
285 conditions (figure 1) and these regions showed significantly greater increase in ALFF after
286 psilocybin therapy versus before (figure 1 histograms; panel C). Examining the effects of the
287 psychedelic therapy on each scan type separately revealed lower ALFF in the medial frontal
288 lobe for the resting-state scan after therapy versus before, and increased ALFF in the superior
289 temporal lobe regions and supramarginal gyrus for the music scan after versus before
290 therapy. Patients therefore had higher responses in recognized music and musical emotion-
291 processing brain regions (Koelsch et al., 2018) after the therapy. Furthermore, this increased
292 ALFF-indexed responsiveness to music was mediated by the subjective quality of the
293 psychedelic experience in the therapy session, with the increases in ALFF being significantly
294 correlated with higher levels of (anxious) ego-dissolution, visionary restructuralization,
295 auditory alterations, and vigilance reduction as well as an averaged total or ‘global’ score, all
296 measured by the 5D-ASC questionnaire (Dittrich, 1998; Hasler, Grimberg, Benz, Huber, &
297 Vollenweider, 2004). This suggests a potential causal effect of the drug experience in
298 producing the effects.

299 The finding that music-listening (compared with rest) produces increased LFOs in the
300 superior temporal region (Heschl’s gyrus, and the planum temporale) is unsurprising, as these
301 regions belong to the primary auditory cortex, and are highly specialized for sound
302 perception, including music. What is perhaps more interesting is that responses in these
303 regions were also significantly affected by the therapy in these patients, given that most
304 previous work on musical aesthetics and emotionality has tended to identify reward/limbic
305 regions as being of greater importance for these features (Brown, Gao, Tisdelle, Eickhoff, &
306 Liotti, 2011; Koelsch, 2020; Koelsch & Skouras, 2014; Menon & Levitin, 2005). However,
307 recent work has also strongly made the case that the auditory cortex plays a role in the
308 processing of affective auditory information, and has functional connections with limbic and
309 paralimbic structures (Koelsch et al., 2018). A recent meta-analysis (N=47 studies) has also
310 identified Heschl’s gyrus as being specifically involved in music-evoked emotions, as well as
311 a range of other limbic and reward regions (Koelsch, 2020). These results therefore provide
312 additional convergent evidence that the therapeutic effect of psilocybin is (at least, partly)
313 mediated by the qualities of the acute psychedelic experience, including ‘emotional

314 breakthroughs' which are a key mediator of longer-term psychological effects, including
315 improvements in mental health outcomes (Roseman et al., 2019). Previous work on this
316 cohort of patients is also supportive of this interpretation, showing that changes in the
317 functional connectivity of emotion/reward regions - such as the vmPFC - are meaningfully
318 related to longer-term clinical effects (Carhart-Harris et al., 2017) and that brain responses to
319 emotional face stimuli one day post-treatment show clear increases after the therapy
320 (Roseman et al., 2018), with additional effects on brain connectivity (Mertens et al., 2020);
321 although see Barrett, Doss, Sepeda, Pekar, & Griffiths (2020) for contrasting results after a
322 longer period post-dose. Taken together, it is tempting to infer a greater sensitivity or
323 responsivity to emotional stimuli in complex emotional processing systems post psilocybin
324 therapy; consistent with findings that emotional responsiveness is enhanced post psilocybin
325 therapy (Carhart-Harris et al., 2021).

326 The present study's results also further validate the use of music as an experimental probe
327 stimulus in studies of depression and build upon previous work in this area (e.g. Jenkins *et*
328 *al.*, 2018). The approach used here of a single continuous piece of music contrasted with a
329 resting-state scan is relatively uncommon but provides a novel and rich dataset which can be
330 interrogated with a number of different analysis approaches (Cong et al., 2014). The analysis
331 of LFOs presented here would likely not be possible with a more conventional fMRI design
332 (e.g. relatively short blocks of music separated by silence or non-musical sound). Use of
333 continuous 'naturalistic' stimuli in fMRI is becoming more common (Breakspear & Chang,
334 2020; Maguire, 2012; Sonkusare, Breakspear, & Guo, 2019), with recent results showing that
335 it may have higher test-retest reliability than standard methods (Wang et al., 2017), be more
336 accurately predictive of behavioural phenotypes (Finn & Bandettini, 2021), and have the
337 advantage of superior ecological validity versus e.g., short blocks of music.

338 The post-therapy changes seen in the resting-state scan in the medial frontal lobe are also
339 consistent with previous work showing abnormal medial frontal lobe functioning in
340 depression (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012; Lemogne et al., 2009;
341 Nejad, Fossati, & Lemogne, 2013). The medial PFC has also been implicated in the acute
342 brain action of psychedelics (Carhart-Harris et al., 2012, 2015). Previous work using ALFF
343 methods has identified frontal lobe abnormalities in major depression (Rosenbaum et al.,
344 2020) and in depressed Parkinson's disease patients (Wen, Wu, Liu, Li, & Yao, 2013). The
345 medial frontal lobe has been implicated in the action of selective serotonin re-uptake

346 inhibitors (SSRI) treatment (Di Simplicio, Norbury, & Harmer, 2012; Godlewska, Browning,
347 Norbury, Cowen, & Harmer, 2016; Ma, 2015). Recent work has also shown reductions in
348 medial-frontal connectivity with the amygdala, following psychedelic therapy (Mertens et al.,
349 2020) as well as decreased mPFC-posterior cingulate cortex functional connectivity under
350 psilocybin (Carhart-Harris et al., 2012) but increased mPFC-parietal lobule connectivity after
351 psilocybin therapy for depression (Carhart-Harris et al., 2017). Taken together, these findings
352 converge on medial PFC dysfunction in depression being a key target for psilocybin therapy.

353 Limitations of this study largely relate to its design as an open-label trial with a limited
354 number of subjects and lack of placebo control; these issues will require further trials to
355 adequately address. In the mean ALFF data (see supplementary material) the pattern of high
356 values around the base of the brain where there are many large blood vessels, does suggest a
357 substantial physiological (cardiac, respiratory) component in the signal, despite the de-
358 noising procedures used. However, the experimental design used here effectively controls for
359 these effects, with within-subjects comparisons used for both cross-session and within-
360 session contrasts between the resting and music scans. ALFF measures have high reliability
361 (Li et al., 2012), with physiological effects also showing high temporal stability (Küblböck et
362 al., 2014) and are therefore effectively subtracted out by the within-subjects design. The
363 specificity of the results of contrasts between resting and music scans (figure 1), which
364 specifically highlight the auditory cortex, suggest that this is the case. The related measure
365 fALFF (fractional ALFF; Zou *et al.*, 2008) is somewhat less influenced by physiological
366 effects, but also has significantly lower test-retest reliability (Zuo & Xing, 2014), making it a
367 less suitable measure in this study, which relies on cross-session comparisons.

368 In summary, this study's results suggest that naturalistic music-listening, as well as being a
369 crucial part of the therapy itself (Barrett et al., 2018), is also a potentially useful method for
370 investigating treatment effects in psychedelic-therapy research. Patients in this study showed
371 an enhanced response to music-listening the day after the therapy, as indexed by increased
372 ALFF, and this enhanced response was related to the intensity of the subjective effects felt
373 during the acute psychedelic experience on the high-dose therapy visit. Future work may
374 examine the effects of music with a longer gap separating the last dosing and the post
375 treatment scan, as there are some reasons to believe that different brain changes can be seen
376 one day post-treatment versus after a longer post-treatment period. Nevertheless, these data
377 provide an initial indication of the effects of psychedelic therapy for depression on brain

378 responses to music that will help to enrich our understanding of psilocybin's therapeutic
379 mechanisms as we go forward.

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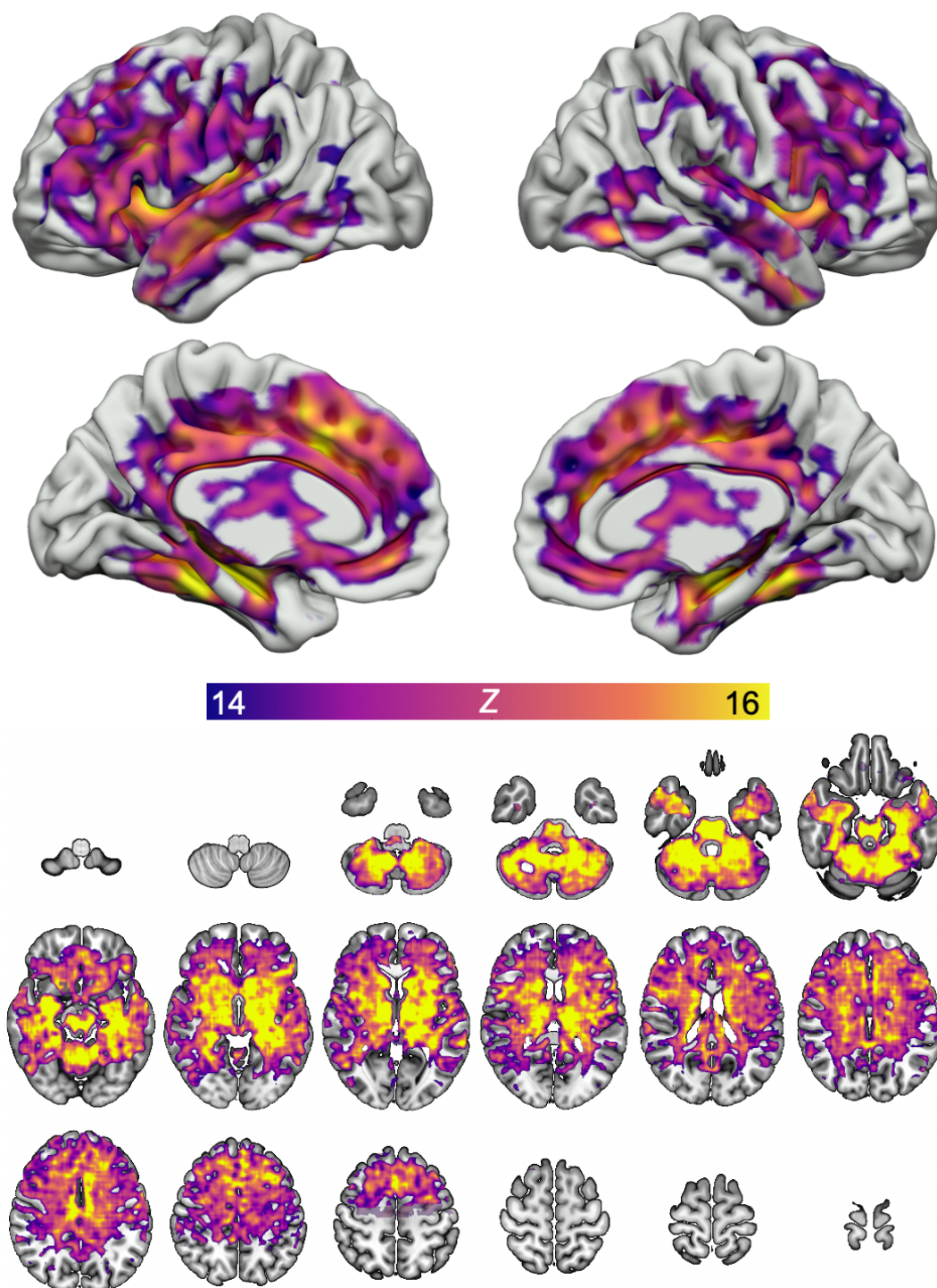
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576 **Supplementary Material**



577

578 Figure S1. Mean ALFF values across all subjects (N=19), and all scans (four scans per
579 subject; music-listening and resting-state scans, before and after therapy). All statistical maps
580 are generated with cluster probability threshold of $Z=2.3$, $p<0.05$, cluster-corrected for
581 multiple comparisons. Images are shown in neurological orientation (left hemisphere = left of
582 the image).

	Music Δ (after - before)		Rest Δ (after - before)	
	Pearson's <i>r</i>	<i>p</i> -value	Pearson's <i>r</i>	<i>p</i> -value
GEMS-3, Sublimity, Day2	0.145	0.565	0.141	0.577
GEMS-3, Vitality, Day 2	0.336	0.173	0.141	0.578
GEMS-3, Unease, Day 2	0.079	0.754	-0.069	0.786

583

584 Table S1. Correlations between the delta (after treatment – before treatment) of ALFF
 585 measures in ROIs and the GEMS-3 scale on day 2 (high-dose treatment day). All correlations
 586 were non-significant (all *p* values > 0.17).

587

	Music Δ (after - before)		Rest Δ (after - before)	
	Pearson's <i>r</i>	<i>p</i> -value	Pearson's <i>r</i>	<i>p</i> -value
QIDS: Baseline	-0.209	0.391	-0.005	0.984
QIDS: 1 Week	-0.108	0.659	-0.068	0.781
QIDS: 2 Weeks	-0.06	0.807	0.058	0.812
QIDS: 3 Weeks	-0.077	0.753	-0.083	0.737
QIDS: 5 Weeks	0.009	0.97	-0.012	0.962
QIDS: 3 Months	0.252	0.298	0.28	0.246
QIDS: 6 Months	0.009	0.971	-0.026	0.915

588

589 Table S2. Correlations between the delta (after treatment – before treatment) of ALFF
 590 measures in ROIs and the Quick Inventory of Depression Symptoms scale at time-points
 591 ranging from baseline (start of the study) to the six-month follow-up. All correlations were
 592 non-significant (all *p* values > ~0.3).

593

	Music Δ (after - before)		Rest Δ (after - before)	
	Pearson's <i>r</i>	<i>p</i> -value	Pearson's <i>r</i>	<i>p</i> -value
5D-ASC: OCEAN	0.294	0.222	0.201	0.41
5D-ASC: DED	0.49	0.033	0.336	0.16
5D-ASC: VRS	0.557	0.013	0.407	0.084
5D-ASC: AUA	0.545	0.016	0.307	0.2
5D-ASC: VIR	0.613	0.005	0.406	0.084
5D-ASC: Mean	0.621	0.005	0.411	0.08

594

595 Table S3. Correlations between the delta (after treatment – before treatment) of ALFF
596 measures in ROIs and the 5-dimensional altered states of consciousness (5D-ASC) scale
597 acquired during the second (high-dose) dosing visit. OCEAN = “Oceanic boundlessness”;
598 DED = “Ego-dissolution”; VRS = “Visionary restructuralization”; AUA = “Auditory
599 alterations”; VIR = “Vigilance reduction”. MEAN = Mean of all five sub-scales. Significant
600 correlations ($p < 0.05$) are highlighted with bold text. The VIR and mean result survive a
601 family-wise corrected p value threshold of 0.008.

602