Supplementary Material

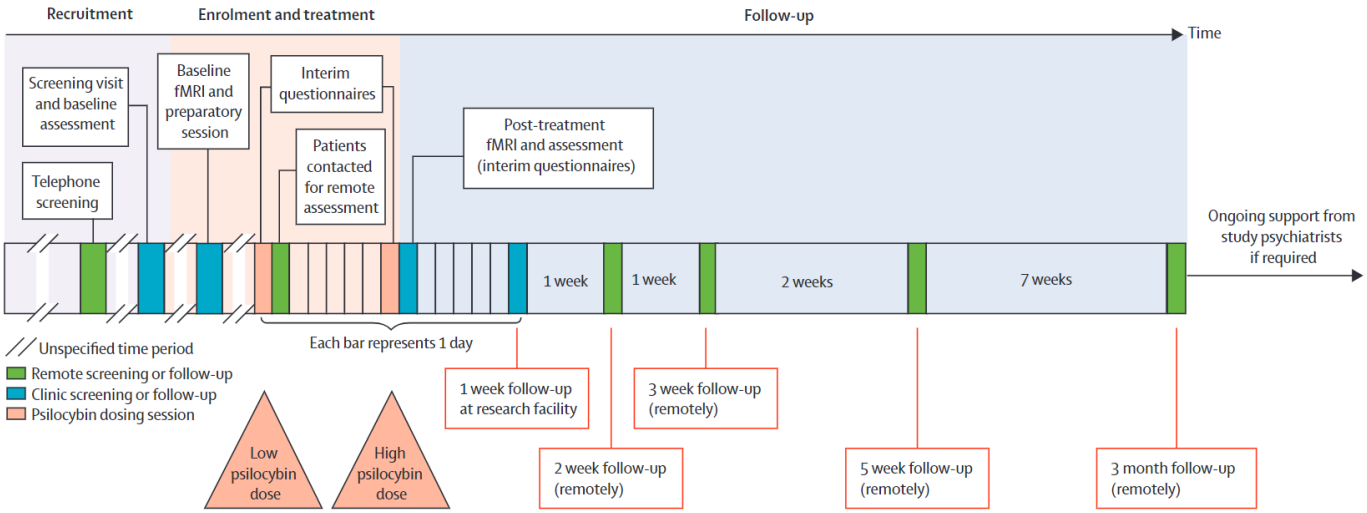

Figure 1. Trial design and intervention schedule. Adopted from Carhart-Harris et al. (2916).

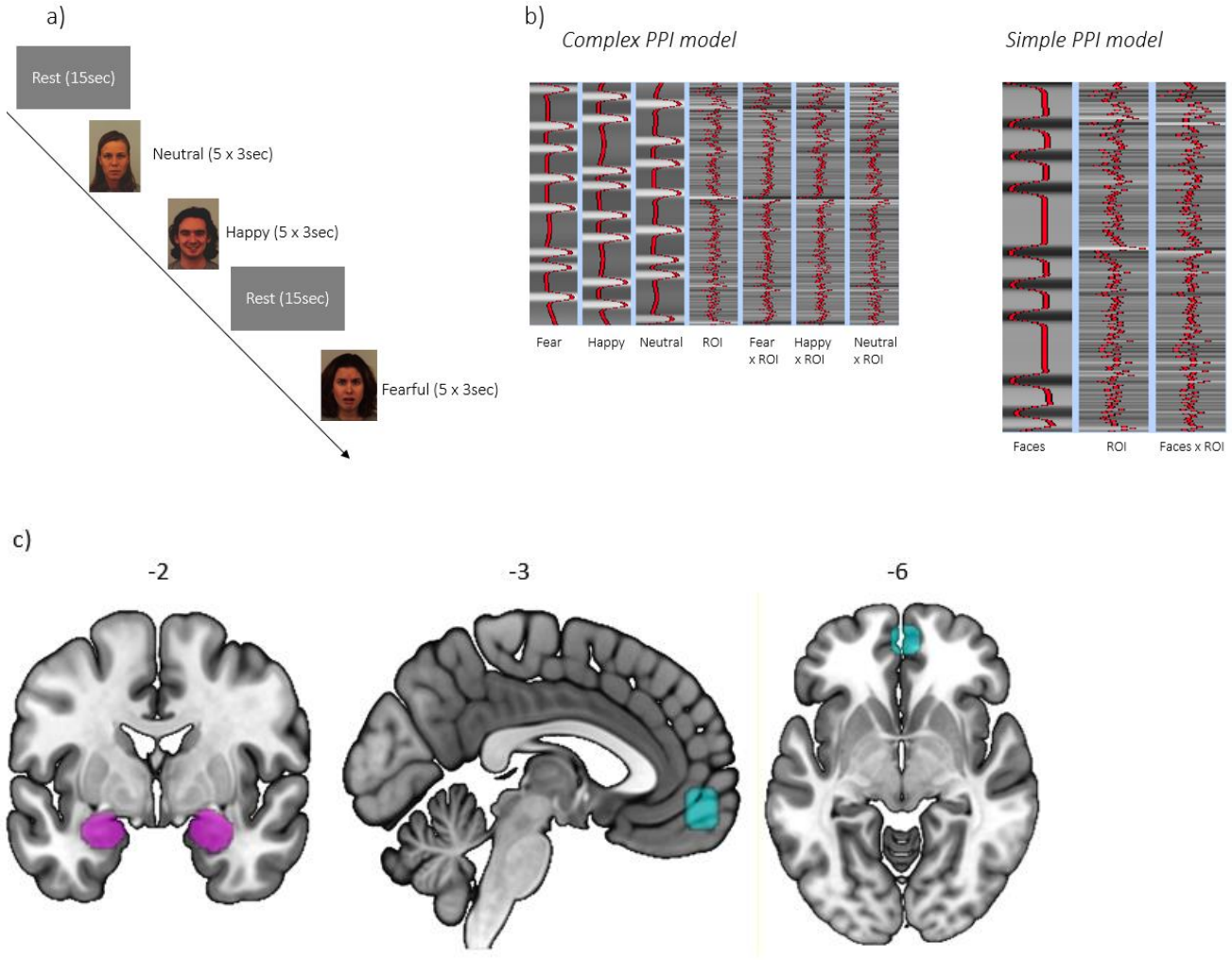

Figure 2. fMRI block-design emotional face processing task and PPI model

a) Patients were presented with faces with happy, fearful or neutral expressions selected from the Karolinska Directed Emotional Faces set (Goeleven et al., 2008) within a paradigm that lasted 8 minutes in total.

b) Two different PPI models were analysed. The first was a simple one only including a single face (irrespective of emotional expression) regressor, the ROI and their interaction. The second was a complex one differentiating between different facial expressions, analysing functional connectivity of our ROI's separately for different facial expressions (happy, neutral, fearful).

c) Depiction of the two ROI's, the bilateral amygdala (pink) and the vmPFC (blue)

Note: PPI = Psychophysiological Interaction, vmPFC = ventromedial prefrontal cortex, ROI = region of interest

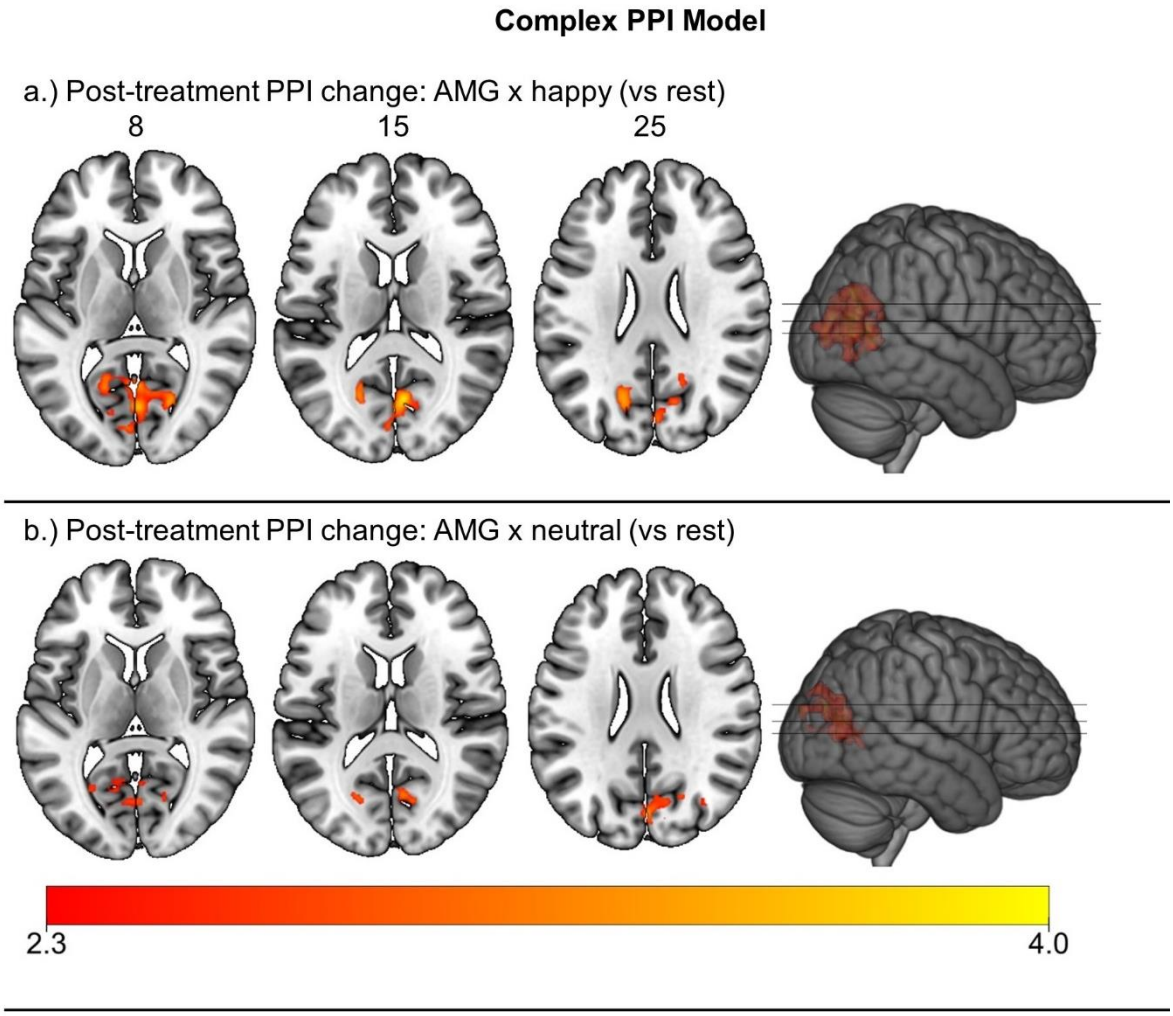

Figure 3. Results of the psychophysiological interaction whole-brain analysis comparing amygdala functional connectivity when processing different facial expressions with rest (complex model) before and after treatment with psilocybin. Regions with increased connectivity (after > before) are depicted in red (cluster-corrected, $p < 0.05$, $Z > 2.3$). No significant clusters were identified **f**or the AMG x fearful (vs rest) contrast.

Note: FC = functional connectivity, AMG = amygdala, PPI = psychophysiological interaction

Analyses of relation to clinical outcomes

Table 1

Exploratory Analyses of Relation of amygdala and vmPFC functional connectivity to depression (BDI) and rumination (RRS) levels at three-months post-treatment

		BDI								RRS			
ROI	**FC cluster**	**Raw Score**		**Change**		**Response**		**Remission**		**Raw score**		**Change**	
		3 months				3 months (n = 9)		3 months (n = 6)		3 months			
		r	*p*	*r*	*p*	*t*	*p*	*t*	*p*	*r*	*p*	*r*	*p*
Amygdala (bilat.) vmPFC	Parietal-occipital after	-.27	.257			-0.20	.845	-2.02	.059	-.38	.104		
	Parietal-occipital ΔBeta			.12	.615	-0.34	.738	-1.58	.132			.082	.740
	Amygdala (R) after	-.12	.638			-.047	.963	.88	.390	-.093	.706		
	Amygdala (R) ΔBeta			.34	.161	-1.02	.324	-.19	.853			.24	.329
	Parietal-occipital after	-.23	.354			.19	.619	-2.73	.014	-.28	.245		
	Parietal-occipital ΔBeta			.17	.49	-.90	.381	-3.93	.001**			.26	.291

Note: FC = functional connectivity; * = significant at α = .05, ** = significant at α = .01; ΔBeta = after – before, clinical "Change" = before - after

Table 2

Exploratory Analyses on Relation of amygdala and vmPFC functional connectivity to depression (QIDS-16-SR) scores at multiple time points post-treatment

ROI	**FC cluster**	**QIDS-SR-16 Raw score**													
		1 day		1 week		2 weeks		3 weeks		5 weeks		3 months		6 months	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Amygdala (bilat.)	Parietal-occipital after	-.33	.172	-.25	.303	-.42	.074	-.36	.126	-.25	.297	-.19	.425	-.44	.063
	Parietal-occipital ΔBeta	-.26	.282	-.11	.641	-.28	.249	-.303	.207	-.13	.584	-.11	.663	-.22	.373
vmPFC	Amygdala (R) after	.24	.331	.28	.247	.23	.354	.12	.635	.009	.972	-.098	.690	-.11	.669
	Amygdala (R) ΔBeta	-.13	.606	-.11	.656	-.13	.584	-.22	.364	-.31	.193	-.37	.118	-.44	.059
	Parietal-occipital after	-.37	.120	-.33	.170	-.36	.132	-.22	.365	.011	.966	-.16	.506	.021	.932
	Parietal-occipital ΔBeta	-.47	.041*	-.43	.067	-.53	.021*	-.43	.065	-.19	.442	-.25	.300	-.012	.961

Note: FC = functional connectivity; * = significant at α = .05; ΔBeta = after – before

Results of additional PPI analyses with the left and right amygdala added as seed-ROI separately

Table 3

Summary of the results of supplementary seed-to-voxel psychophysiological interaction analyses comparing functional connectivity during face processing (irrespective of facial expression) with rest (simple model)

ROI	Contrasts	Functional Connectivity	Regions	Volume (mm^3)	MNI_152 coordinates			Difference max (z)	Sig
					x	y	z		
Right amygdala	AMG (R)	↓	**Lateral occipital cortex (L)**	532	-40	-79	27	3.80	**
			Occipital pole (L)		-30, -24	-90, -94	32, 24	3.42, 3.19	***
		↑	**Insula (L)**	851	-40	5	-2	3.77	***
			Frontal operculum (L)		-46, -42	10, 16	2, 0	3.77, 3.69	***
			Temporal pole (L)		-46	4	-10	3.54	***
			Superior temporal gyrus (L)		-48	-14	-6	3.33	***
	AMG (R) x Faces (vs rest)	↑	**Lateral occipital cortex (R)**	349	38	-74	30	3.44	*
			Precuneus (R)		22	-70	32	3.44	***
			Intracalcarine cortex	1633	-4	-76	17	3.89	***
			Cuneus		2	-80	26	3.88	***
			Occipital pole (L)		-4, -12	-100, -98	16, 20	3.48, 3.47	***
Right Amygdala subpart[1]	AMG (R) FC	↑	**Cingulate**	485	1	34	3	3.83	**
			Subcallosal cortex (L/R)		-6/4	26/26	-2/2	3.83/3.28	***
			Paracingulate gyrus		-2, -4	50, 44	-2, -4	3.10, 2.89	***, **
	AMG (R) x Faces (vs rest)	↓	**Middle temporal gyrus (L)**	296	-56	-13	-13	3.94	*
			Superior temporal gyrus (L)		-56, -52	-10, -2	-10, -12	3.94, 2.62	***, **
			Temporal pole (L)		-48	-14	-2	3.13	***
			Inferior temporal gyrus		-50	-14	-22	2.67	**
		↑	**Cuneus**	1476	1	-78	20	3.91	***
			Intracalcarine cortex (L/R)		-6/18	-86/-70	6/12	3.61/3.38	***
			Occipital pole		12	-92	22	3.46	***
			Supracalcarine cortex		0	-88	10	3.37	***
			Lateral occipital cortex		18	-84	36	3.36	***

Left Amygdala	AMG (L) FC	↓	**Lateral occipital cortex (R)**	324	45	-61	32	3.75	*
			Angular gyrus (R)		44	-48	36	2.74	**
			Precuneus	615	3	-57	37	3.56	***
			Cingulate (R)		8	-46	38	3.07	**
		↑	**Insula (L)**	890	-33	9	2	3.78	***
			Frontal Operculum (L)		-40, -32	16, 26	0, 8	3.78, 3.38	***
			Caudate (L)		-14	10	12	3.28	***
	AMG (L) x Faces (vs rest)	↑	**Supracalcarine cortex**	715	4	-76	14	3.35	***
			Intracalcarine cortex		4, 2	-64, -72	14, 8	3.35, 3.27	***
			Precuneus (R)		22	-70	32	3.05	**

Note: vmPFC = ventromedial prefrontal cortex, AMG = amygdala, R = right hemisphere, L = left hemisphere, ↑ / ↓= increased (after > before)/decreased (before > after) after psilocybin; Overall clusters are depicted in bold, local maxima in simple font; MNI_152 coordinates are given for the Centre of Gravity (COG) of overall clusters and of the voxel with maximum intensity (z-max) for local maxima; significance values are reported for the overall cluster and the z-max of local maxima

* z > 2.3 (cluster-corrected, p < .05)

** z > 2.3 (cluster-corrected, p < .01)

*** z > 2.3 (cluster-corrected, p < .001)

[1] part of the right amygdala showing significantly higher activation during fearful vs neutral faces after treatment with psilocybin (Roseman et al., 2018)