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The role of the serotonin 2A receptor in the fabric and modulation of personal meaning in LSD-induced states

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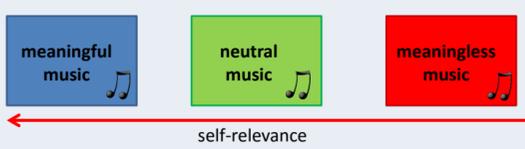
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Introduction

- Abnormalities in the **attribution of personal relevance** to stimuli are critical features of many psychiatric disorders [1].
- The **neuropharmacological substrates** enabling meaningful and personally relevant experiences are largely unknown.
- **Lysergic acid diethylamide (LSD)** is a prototypical hallucinogen which has high affinity at **serotonin** (5-HT) and dopamine receptors (R) and increases the sense of meaning of objects [2].
- **Ketanserin** is a selective **5-HT2AR** antagonist .

Objective

To investigate the role of the **5-HT2AR system** in **personal meaning attribution** by applying pharmacological functional brain imaging using LSD with and without pre-treatment with ketanserin.

Methods

| Design	• Double-blind, randomized, cross-over, placebo-controlled
Drugs	• Placebo + Placebo (Pla) • Placebo + LSD (100µg) (LSD) • Ketanserin (40mg) + LSD (100µg) (Ket+LSD)
Task	meaningful music / neutral music / meaningless music ← self-relevance • 20s of music followed by a rating and a jittered ITI
Participants	• 22 healthy volunteers
Dependent variables	• FMRI: BOLD contrast • Meaningfulness Ratings • Altered States of Consciousness Questionnaire
Statistics	• General Linear Model as implemented in SPM12 • Repeated-measures Analyses of Variance (rmANOVA)

Results Subjective Drug Effects

- LSD increased ratings on all 5D-ASC scales compared to Pla and Ket+LSD (all $p < 0.05$) expect for spiritual experience and anxiety.
- **Pla and LSD+Ket scores did not differ** on any scale (all $p > 0.90$).
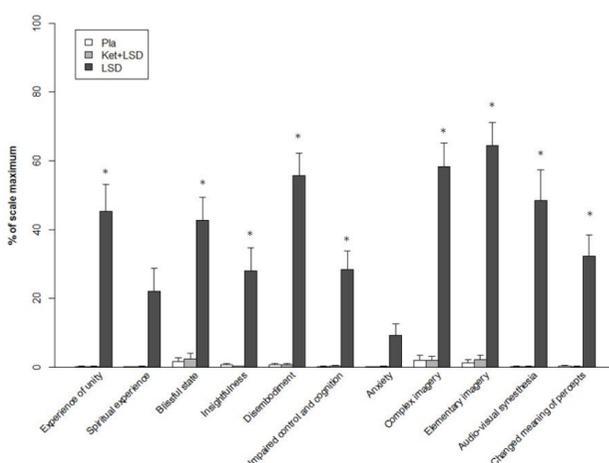
Fig. 1. 5D-ASC scores are expressed as percent of the scale maximum. Data are expressed as means + SEM (n = 22). *indicate significant ($p < 0.05$, Bonferroni corrected) differences between LSD and Pla, and LSD and Ket+LSD treatment conditions.

Results Rating

Meaningfulness ratings were **increased for meaningless** and **neutral** music under LSD compared to both Pla and Ket+LSD (all $p<0.05$) (Fig. 1).
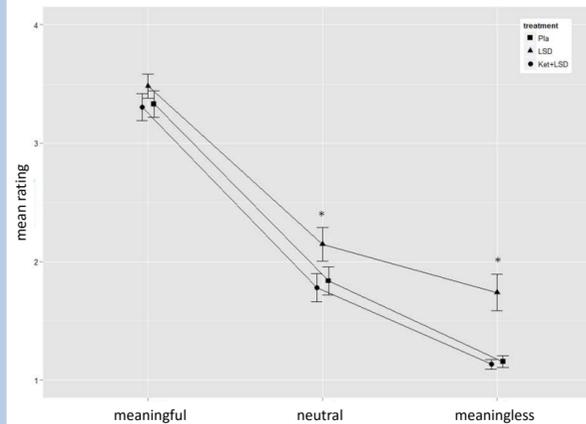

Fig 2. Data are expressed as means ± the standard error of the mean. *indicate significant differences between LSD and Pla, and LSD and Ket+LSD ($p<0.05$, Bonferroni corrected, n = 22).

Results fMRI

Meaningless music compared to neutral and meaningful music was associated with increased BOLD signal in **medial and lateral frontal brain areas in the LSD** condition compared to both Pla and Ket+LSD conditions (all $p<0.05$, FWE corrected, Fig. 3 & 4).
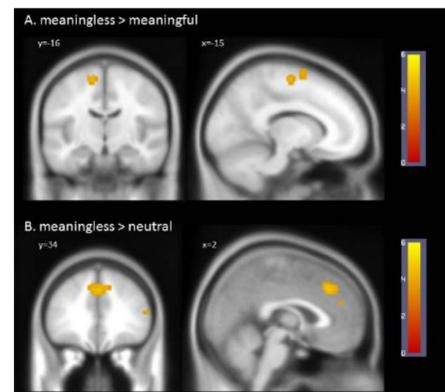
Fig 3. LSD > Pla comparison. A) "meaningless > meaningful" contrast B) "meaningless > neutral" contrast displayed at $p < 0.001$ (uncorrected); n=22.
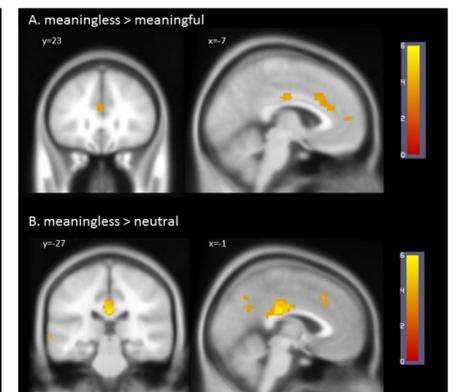
Fig 4. LSD > Ket+LSD comparison. A) "meaningless > meaningful" contrast B) "meaningless > neutral" contrast displayed at $p < 0.001$ (uncorrected); n=22.

Conclusion and implication

- **LSD increased the attribution of personal relevance** to previously meaningless stimuli.
- This effect appears to be attributable to **5-HT2AR stimulation**.
- LSD-induced effects were **blocked by 5-HT2AR antagonism.**
- The current results emphasize the pivotal role of the **5-HT2AR** in the **generation of personal meaning** in **medial and lateral frontal brains structures** implicated in self-referential processes.

These findings may be relevant for increasing our understanding of the **biochemical underpinnings of personal meaning processing** and may reveal **prospective targets** in the treatment of psychiatric illnesses characterized by alterations in meaning attribution.

References:
[1] Moeller, S.J. & Goldstein, R.Z. Impaired self-awareness in human addiction: deficient attribution of personal relevance. Trends Cogn Sci 18, 635-641 (2014).
[2] Schmid, Y., et al. Acute Effects of Lysergic Acid Diethylamide in Healthy Subjects. Biol Psychiatry 78, 544-553 (2015).