

## Publication

Activation of serotonin 2A receptors underlies the psilocybin-induced effects on  $\alpha$  oscillations, N170 visual-evoked potentials, and visual hallucinations

### JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

**ID** 3720882

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**Year** 2013

**Title** Activation of serotonin 2A receptors underlies the psilocybin-induced effects on  $\alpha$  oscillations, N170 visual-evoked potentials, and visual hallucinations

**Journal** The Journal of neuroscience : the official journal of the Society for Neuroscience

**Volume** 33

**Number** 25

**Pages / Article-Number** 10544-10551

**Mesh terms** Adult; Alpha Rhythm, drug effects; Analysis of Variance; Consciousness, drug effects; Data Interpretation, Statistical; Double-Blind Method; Electroencephalography, drug effects; Evoked Potentials, Visual, drug effects; Female; Hallucinogens, pharmacology; Humans; Ketanserin, pharmacology; Male; Photic Stimulation; Psilocybin, pharmacology; Psychometrics; Psychomotor Performance, drug effects; Reaction Time, physiology; Receptor, Serotonin, 5-HT<sub>2A</sub>, drug effects; Serotonin Antagonists, pharmacology; Serotonin Receptor Agonists, pharmacology; Surveys and Questionnaires; Young Adult  
Visual illusions and hallucinations are hallmarks of serotonergic hallucinogen-induced altered states of consciousness. Although the serotonergic hallucinogen psilocybin activates multiple serotonin (5-HT) receptors, recent evidence suggests that activation of 5-HT<sub>2A</sub> receptors may lead to the formation of visual hallucinations by increasing cortical excitability and altering visual-evoked cortical responses. To address this hypothesis, we assessed the effects of psilocybin (215  $\mu$ g/kg vs placebo) on both  $\alpha$  oscillations that regulate cortical excitability and early visual-evoked P1 and N170 potentials in healthy human subjects. To further disentangle the specific contributions of 5-HT<sub>2A</sub> receptors, subjects were additionally pretreated with the preferential 5-HT<sub>2A</sub> receptor antagonist ketanserin (50 mg vs placebo). We found that psilocybin strongly decreased prestimulus parieto-occipital  $\alpha$  power values, thus precluding a subsequent stimulus-induced  $\alpha$  power decrease. Furthermore, psilocybin strongly decreased N170 potentials associated with the appearance of visual perceptual alterations, including visual hallucinations. All of these effects were blocked by pretreatment with the 5-HT<sub>2A</sub> antagonist ketanserin, indicating that activation of 5-HT<sub>2A</sub> receptors by psilocybin profoundly modulates the neurophysiological and phenomenological indices of visual processing. Specifically, activation of 5-HT<sub>2A</sub> receptors may induce a processing mode in which stimulus-driven cortical excitation is overwhelmed by spontaneous neuronal excitation through the modulation of  $\alpha$  oscillations. Furthermore, the observed reduction of N170 visual-evoked potentials may be a key mechanism underlying 5-HT<sub>2A</sub> receptor-mediated visual hallucinations. This change in N170 potentials may be important not only for psilocybin-induced states but also for understanding acute hallucinatory states seen in psychiatric disorders, such as schizophrenia and Parkinson's disease.

**Publisher** SOC NEUROSCIENCE

**ISSN/ISBN** 1529-2401

**edoc-URL** <https://edoc.unibas.ch/63103/>

**Full Text on edoc** No;

**Digital Object Identifier DOI** 10.1523/JNEUROSCI.3007-12.2013

**PubMed ID** <http://www.ncbi.nlm.nih.gov/pubmed/23785166>

**ISI-Number** WOS:000320596400033

**Document type (ISI)** Article