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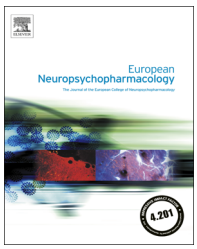

Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans ☆

José Carlos Bouso[a,b], Fernanda Palhano-Fontes[c], Antoni Rodríguez-Fornells[d,e,f], Sidarta Ribeiro[c], Rafael Sanches[g], José Alexandre S. Crippa[g], Jaime E.C. Hallak[g], Draulio B. de Araujo[c], Jordi Riba[a,h,i,*]

[a]*Human Neuropsychopharmacology Group, Sant Pau Institute of Biomedical Research (IIB-Sant Pau), C/Sant Antoni María Claret, 167, 08025 Barcelona, Spain*
[b]*International Center for Ethnobotanical Education, Research & Service, Barcelona, Spain*
[c]*Brain Institute/Hospital Universitario Onofre Lopes, Federal University of Rio Grande do Norte, Natal, Brazil*
[d]*Cognition and Brain Plasticity Group, IDIBELL (Bellvitge Biomedical Research Institute), L'Hospitalet de Llobregat, Barcelona 08097, Spain*
[e]*Department of Basic Psychology, University of Barcelona, Barcelona 08035, Spain*
[f]*Catalan Institution for Research and Advanced Studies, ICREA, Barcelona, Spain*
[g]*Neuroscience and Behaviour Department, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil*
[h]*Centre d'Investigació de Medicaments, Servei de Farmacologia Clínica, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[i]*Departament de Farmacologia i Terapèutica, Universitat Autònoma de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain*

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Abstract
Psychedelic agents have a long history of use by humans for their capacity to induce profound modifications in perception, emotion and cognitive processes. Despite increasing knowledge of the neural mechanisms involved in the acute effects of these drugs, the impact of sustained psychedelic use on the human brain remains largely unknown. Molecular pharmacology studies have shown that psychedelic 5-hydroxytryptamine $(5HT)_{2A}$ agonists stimulate neurotrophic and

☆Cortical thickness and psychedelic drugs.

*Corresponding author at: Human Neuropsychopharmacology Group, Sant Pau Institute of Biomedical Research (IIB-Sant Pau), C/Sant Antoni María Claret, 167, 08025 Barcelona, Spain.
Tel.: +34 93 556 5518; fax: +34 93 553 7855.
E-mail address: jriba@santpau.cat (J. Riba).

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transcription factors associated with synaptic plasticity. These data suggest that psychedelics could potentially induce structural changes in brain tissue. Here we looked for differences in cortical thickness (CT) in regular users of psychedelics. We obtained magnetic resonance imaging (MRI) images of the brains of 22 regular users of ayahuasca (a preparation whose active principle is the psychedelic 5HT$_{2A}$ agonist *N,N*-dimethyltryptamine (DMT)) and 22 controls matched for age, sex, years of education, verbal IQ and fluid IQ. Ayahuasca users showed significant CT differences in midline structures of the brain, with thinning in the posterior cingulate cortex (PCC), a key node of the default mode network. CT values in the PCC were inversely correlated with the intensity and duration of prior use of ayahuasca and with scores on self-transcendence, a personality trait measuring religiousness, transpersonal feelings and spirituality. Although direct causation cannot be established, these data suggest that regular use of psychedelic drugs could potentially lead to structural changes in brain areas supporting attentional processes, self-referential thought, and internal mentation. These changes could underlie the previously reported personality changes in long-term users and highlight the involvement of the PCC in the effects of psychedelics.

1. Introduction

Psychedelics, have been used since ancient times by geographically distant human groups for their capacity to induce profound modifications in the ordinary state of consciousness and to generate spiritually meaningful experiences (Schultes, 1979). The ancient practice of ritual psychedelic use not only survived well into the twentieth century, but has expanded beyond indigenous use following contact of previously isolated groups with foreigners (Tupper, 2008).

One of the most interesting contemporary adaptations of psychedelic use is the syncretism observed in Brazilian religious groups that consume ayahuasca, an infusion of the plants *Banisteriopsis caapi* and *Psychotria viridis*. These ayahuasca religions have expanded in the last decades, and it is estimated that around 20,000 people in 23 countries currently take ayahuasca regularly within a ritual context. Typically, participants attend ayahuasca-using rituals once every other week for many years (Grob et al., 1996).

Regarding the active principles present in ayahuasca, one of the plants, *P. viridis*, contains *N,N*-dimethyltryptamine (DMT). DMT is structurally related to serotonin and acts as a 5-HT$_{2A}$ receptor agonist (González-Maeso and Sealfon, 2009). DMT elicits intense, short-acting psychedelic effects when administered intravenously (Strassman et al., 1994) but is rapidly degraded by monoamine-oxidase (MAO) when orally ingested. Interestingly, DMT is rendered orally active by the MAO-inhibiting β-carboline alkaloids found in the other plant, *B. caapi*, used in ayahuasca (Riba et al., 2001).

Molecular pharmacology studies have shown that psychedelic 5-HT$_{2A}$ agonists stimulate expression of immediate early genes that encode transcription factors, such as c-fos (Frankel and Cunningham, 2002), egr-1 and egr-2 (González-Maeso et al., 2007). They also increase the expression of the brain-derived neurotrophic factor (Gewirtz et al., 2002). Activation of these transcription factors has been associated with synaptic plasticity (O'Donovan et al., 1999), and cognitive processes such as memory (Jones et al., 2001) and attention (DeSteno and Schmauss, 2008).

Despite increasing research into the acute effects of psychedelics and the growing interest for their potential use as therapeutic agents (Grob et al., 2011), little is known about the impact of sustained psychedelic use on the human brain. Based on the available molecular data mentioned above, we postulated that repeated exposure to psychedelics would correlate with changes in brain structure. To test this hypothesis we investigated brain cortical thickness (CT) in chronic psychedelic drug users who had minimal exposure to other drugs and their matched controls.

2. Experimental procedures

2.1. Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee at Hospital de Sant Pau (Barcelona, Spain). All participants provided written informed consent to participate in the study.

2.2. Participants

A group of 22 Spanish ayahuasca users and 22 controls were selected for the study. Ayahuasca users were Santo Daime church members who regularly participated in the rituals and were contacted directly by the researchers. Inclusion criteria were: (a) use of ayahuasca at least 50 times in the previous two years; (b) no personal history of psychiatric or neurological disorders; (c) lifetime use of cannabis on twenty occasions or less; (d) lifetime use of other drugs on ten occasions or less; and (e) no use of ayahuasca or other drugs for two weeks before scan, verified by urine toxicology test. The use of ayahuasca of 50 times in two years is a frequency of use of once every other week, which is typical for the Santo Daime church. To rule out a history of psychiatric and neurological disorders, users and controls were interviewed by a clinical psychologist (JCB). Study participants were specifically questioned if they had suffered from depression, psychotic disorders, drug dependence, loss of consciousness, or seizures at any time in their lives. Additionally, at the time of scanning, the structural MRI images were assessed by a neuroradiologist to rule out any CNS anomalies. The two participant groups were matched for sex, age, years of education, and verbal and fluid intelligence quotient (IQ). Each group comprised six male and 16 female participants. The verbal IQ test used was a Spanish version of the NART (Nelson and O'Connell, 1978), known as TAP—"Test de Acentuación de Palabras" ("Word Accentuation Test") (DelSer et al., 1997). The fluid IQ test