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SCIENZE COGNITIVE

a cura di
DONATA CHIRICÒ

Progettare la cognizione

Nuove prospettive di ricerca interdisciplinare



(CORISCO)

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Mauro Cavarra, Alessandra Falzone, Carmela Mento

Relevant issues in psychedelic-assisted psychotherapy research

Abstract

Preliminary results in the field of cognitive science, consciousness research, neuropsychology and psychopharmacology, have reignited interest in psychedelics after a 3-decade long hiatus. This class of substances - which include compounds such as psilocybin, LSD, ayahuasca and DMT - have shown interesting effects in several areas of functioning classically investigated by the sciences of the mind. Psychedelic research, in fact, holds a unique position at the intersection between classical cognitive science, neuroscience and clinical research. The present work aims at summarising the state of knowledge and at highlighting relevant areas that are instrumental to the understanding and advancement of research in the field. After an introduction aimed at explaining what psychedelics are and how they work, we will discuss their suggested mechanism of action, the importance of the blinding problem in modern age RCTs.

Keywords

Psychedelics, Psilocybin, LSD, Psychedelic-assisted psychotherapy, Neuroplasticity

Riassunto

Alcuni risultati preliminari nel campo delle scienze cognitive, della ricerca sulla coscienza, della neuropsicologia e della psicofarmacologia hanno riaperto l'interesse verso la ricerca sugli psichedelici dopo una pausa durata circa 30 anni. Tale classe di composti - che include sostanze

come psilocibina, LSD e DMT - ha mostrato effetti interessanti in numerose aree legate alle scienze della mente. La ricerca psichedelica, infatti, ricopre una posizione unica all'incrocio tra le scienze cognitive classiche, le neuroscienze e la ricerca clinica. Il presente lavoro mira a riassumere lo stato attuale delle conoscenze in questo campo, sottolineando gli aspetti più salienti e quelli che maggiormente necessitano sviluppo. In seguito ad una introduzione volta a spiegare cosa sono gli psichedelici, discuteremo dei loro effetti, dei loro supposti meccanismi d'azione e dell'urgenza di risolvere il cosiddetto "blinding problem" nei moderni RCT.

Parole Chiave

Psichedelici, Psilocibina, LSD, Psicoterapia psichedelici-assistita, Neuro plasticità

1. Introduction: the second wave of psychedelic research

The current interest on psychedelics is substantially driven by very promising clinical results with almost no recorded adverse event or side effect in appropriately screened participants (Johnson, Richards, and Griffiths 2008; Richards 2015; Carhart-Harris *et al.* 2016; Roseman, Nutt, Carhart-Harris 2017; Carhart-Harris *et al.* 2018). Such results expand on what was previously observed in a) end-of-life settings (Grob *et al.* 2011; Griffiths *et al.* 2016; Ross *et al.* 2016); b) tobacco addiction (Garcia-Romeu, Griffiths, Johnson 2014; Johnson, Garcia-Romeu, Griffiths 2017); c) alcohol addiction (Bogenschutz *et al.* 2015). While these results appear very promising, a relevant portion of patients do not seem to fully benefit from them (Nutt, Erritzoe, Carhart-Harris 2020) and future research should focus on better understanding the cognitive and neuropsychological bases of these effects to gain greater insight on consciousness, states of consciousness and improve response rates and stability of clinical gains.

1.1. What are psychedelics?

From a neurochemical standpoint, psychedelics are agonists or partial agonists at the serotonin 5HT_{2A} receptors that induce «states of altered perception, thought, and feeling that are not experienced

otherwise except in dreams or at times of religious exaltation» (Jaffe 1990). These effects were known to man since primordial times and were often sought in ceremonial contexts (Wasson, Ingalls 1971).

1.1.1. Lysergic Acid Diethylamide (LSD)

LSD is naturally occurring in ergot fungi and produces intense psychedelic experiences often of mystical and spiritual nature. Its effects are mediated by partial agonism at the 5-HT_{2A} receptor, binding to the 5-HT_{1A}, 5-HT_{2C}, and 5-HT_{2B} receptors, and at dopamine D2 receptors. Users often report loss of identification with one's ego (Pahnke 1969), insight, broadening of consciousness, an increase of thought associations and the emergence of new interpretations concerning oneself, one's environment and relationships (Gasser *et al.* 2014). The 1970 Controlled Substances Act halted all research on LSD and other psychedelics. The consequences of these reforms led to the criminalisation of such promising compounds. Potential clinical applications include treatment of addictions (Smith 1958), end-of-life distress (Pahnke 1969; Gasser *et al.* 2014), pain management (Ramaekers *et al.* 2020), the enhancement of neuroplasticity (Ly *et al.* 2018).

1.1.2. Psilocybin

Psilocybin is found in mushroom species and has been used for centuries in ritual contexts especially in Central and South America (Schultes, Hofmann 1992). It is metabolized into psilocin, a partial agonist of the 5-HT_{2A} receptor which also binds to the 5-HT_{2C}, 5-HT_{1A} and 5-HT_{1B}. Its effects last between 3 and 6 hours and include changes in sensory perceptions, synesthesia, euphoria, hallucinations and illusions (Nicholas *et al.* 2018) along with possible unpleasant effects such as anxiety, nausea, headaches (Griffiths *et al.* 2016). Future clinical applications may include treatment of treatment-resistant depression (TRD; Carhart-Harris *et al.* 2016), obsessive-compulsive disorder (OCD), end-of-life anxiety (Grob *et al.* 2011; Griffiths *et al.* 2016; Ross *et al.* 2016) and substance use disorder (SUD; Johnson *et al.* 2014; Bogenschutz *et al.* 2015).

1.1.3. 3,4-Methylenedioxymethamphetamine (MDMA)

MDMA is a phenethylamine that was originally used as a hemostatic drug and was later adopted by psychotherapists as an adjunct to psychotherapy (Holland 2001). The drug then began being synthesised and sold for recreational purposes and became known as *ecstasy*. MDMA is considered an *entactogen* rather than a classic psychedelic given the increase in extraversion, empathy, sociability and positive mood it produces. These effects are mediated by partial agonism of serotonin receptors (5-HT_{2A}, 5-HT_{1A}, and 5-HT_{2C}), and increase in blood concentrations of oxytocin (Kuypers *et al.* 2017; Simmler, Liechti 2018). Investigators tested its effectiveness in conjunction with psychotherapy on PTSD (Mithoefer *et al.*, 2018), a condition in which patients display hyperarousal symptoms, intrusive re-experiencing of traumatic experiences and avoidance behaviors (Mithoefer *et al.*, 2018). Results show improvements in clinically measures such as symptom intensity and pervasiveness.

1.1.4. Ayahuasca

Ayahuasca is a decoction, originally used by indigenous Amazon communities in ceremonial settings, obtained by combining the banisteriopsis caapi vine and plants containing the 5-HT_{2A} receptor agonist DMT (Riba *et al.* 2001; McKenna, Riba 2018). Its effects include visual and auditory hallucinations, altered sensorium, modified spatial perceptions, euphoria and mystical experiences (Kometer, Vollenweider 2018). Experimental and naturalistic studies show that it produces stable adaptive changes in psychopathology scores (Sanchez, de Lima Osório, Dos Santos, *et al.* 2016) and cognitive functioning (Kuypers *et al.* 2016).

2. Neuroplasticity and cognitive flexibility

Neuroplasticity can be defined as «the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections»

(Mateos-Aparicio, Rodríguez-Moreno 2019). In fact, chronic negative affect is associated with lower levels of brain derived neurotrophic factor (BDNF; Sen, Duman, Sanacora 2008) and impaired functional integration in crucial areas involved in the regulatory control of affect-eliciting stimuli such as the prefrontal cortex and structures pertaining to the limbic system (Joormann 2010; Gotlib, Joormann 2010; Autry *et al.* 2011; Duman *et al.* 2016). Cognitive flexibility is continuously recruited along daily life (Eshet 2004), it is considered the cornerstone of cognitive control together with inhibition and working memory (Diamond 2013) and its disruption is involved in the onset and maintenance of a wide spectrum of neurodevelopmental conditions (Morris, Mansell 2018). Owing to efforts spent in cognitive science research which aimed at bridging the gap between neurobiological correlates, cognitive performance and everyday functioning, we can confidently say that cognitive flexibility and psychological health are both closely linked to neuroplasticity (Kashdan, Rottenberg 2010). Recent research showed that serotonergic psychedelics are able to induce long-lasting antidepressant and anxiolytic effects (Bouso *et al.* 2008; Grob *et al.* 2011; Mithoefer *et al.* 2013; Oehen *et al.* 2013; Sanchez, de Lima Osório, dos Santos, *et al.* 2016; Carhart-Harris, Goodwin 2017), gene expression leading to the production of BDNF (Vaidya *et al.* 1997; Nichols, Sanders-Bush 2002; Martin *et al.* 2014) and, structural and functional changes in cortical neurons (Ly *et al.* 2018). This latter result led the authors to coin a new term for this class of compounds: *psychoplastogens*. Within this framework, the relaxed beliefs under psychedelics (REBUS) model was proposed (Carhart-Harris, Friston 2019). It posits that psychedelics work by relaxing high-level priors and making them more sensitive to bottom-up signals which «with the right intention, care provision and context, can help guide and cultivate the revision of entrenched pathological priors.» (ivi). In summary, the modulation of neuroplasticity and, therefore, cognitive flexibility, seem to be the primary mechanism underlying the effect that psychedelics have on consciousness, cognition and mental health.

3. RCTs and ineffective blinding: placebo bug or placebo feature?

One of the hardest methodological challenges that psychedelic research currently faces, in both frames of cognitive science and clinical outcome studies, is the blinding issue. The wide adoption of placebo-controlled trials is justified by the need to disentangle the actual effect of the intervention from that of the so-called *nonspecific factors* such as alliance, expectancy, suggestibility and the placebo effect itself (Kirsch 2013; Zilcha-Mano *et al.* 2018). Nonspecific factors can be defined as those components of the treatment that are not considered specific to a certain pharmacological or non-pharmacological intervention (Gukasyan, Nayak 2021). The overarching principle is that if participants are blinded and therefore unaware of their group assignment, the placebo effect would manifest in similar ways across conditions thus reducing the sources of variability and allowing for a cleaner observation of outcomes (Hendy 2018). Psychedelic research - especially that focused on cognitive, emotional and clinical outcomes - is not easily integrable to such methodological framework given the intensely psychoactive nature of the compounds under scrutiny (Garcia-Romeu, Griffiths, Johnson 2014; James *et al.* 2020). The matter becomes even more complex if we consider that a) psychedelics seem to directly enhance suggestibility (Carhart-Harris *et al.* 2015) and b) set⁸ and setting⁹ seem to be instrumental in achieving clinical improvement (Carhart-Harris, Friston 2019) and in shaping individual experiences (Hartogsohn 2017). Recognising the value of conducting research adhering to modern methodological principles, some authors have proposed ways to overcome this obstacle. First, researchers should use validated tools to measure treatment expectancy such as the Credibility/Expectancy Questionnaire (Borkovec, Nau 1972; Devilly, Borkovec 2000) or the Stanford Expectation of Treatment Scale (Younger *et al.* 2012) to be able to correlate their value with individual experience and clinical outcomes. Second, alliance with the

8 Internal individual factors including beliefs and knowledge about psychedelics, expectations, intention, personality, information (Leary, Metzner, and Dass 1964).

9 External factors related to the cultural, social, relational and physical environment (Leary, Metzner, and Dass 1964).

researcher should be measured in research designs (Zilcha-Mano *et al.* 2018). Third, investigators should report on the effectiveness of masking and pay rigorous attention to all information provided across all steps of recruiting and experimentation (Muthukumaraswamy, Forsyth, Lumley 2021). Fourth, designs should adopt active placebos/comparators (Carhart-Harris, Goodwin 2017; Wilkinson *et al.* 2019).

4. Transformation-based psychiatry: the importance of the context

Pioneers in psychedelic research have emphasized the role of set and setting in determining the quality of the experience and its effects (Richards 2015; Hartogsohn 2017). This vision seems to be supported by evidence showing that a) individual traits and certain mental states (Russ, Elliott 2017) seem to increase the chance of having Mystical Type Experiences (MTE); b) contextual factors such as music seem to promote their occurrence during LSD induced trips (Kaelen *et al.* 2018); c) higher absorption and clear intentions were found to be associated with greater chances of having a MTE as a consequence of the use of psychedelics (Haijen *et al.* 2018); d) having a MTE is associated with better clinical outcomes in patients suffering from TRD (Roseman, Nutt, Carhart-Harris 2017), cancer-related distress (Griffiths *et al.* 2016; Ross *et al.* 2016), tobacco and alcohol addiction (Garcia-Romeu, Griffiths, Johnson 2014; Bogenschutz *et al.* 2015; Johnson, Garcia-Romeu, Griffiths 2017) and with changes in the personality trait of openness (MacLean, Johnson, Griffiths 2011; Lebedev, Kaelen, Lövdén 2016). If we also consider the evidence showing that 5-HT_{2A} agonists promote neuroplasticity (Ly *et al.*, 2018) and environmental sensitivity (Carhart-Harris, Nutt 2017; Carhart-Harris, Friston 2019) it becomes clear that research should focus on finding ways to exploit contextual variables to maximize the effectiveness of psychedelic therapy. This is an especially pressing matter since controlled studies designed to isolate and test key contextual variables have not been yet performed (Carhart-Harris *et al.* 2018). Research, despite some known methodological limitations, indicates that therapeutic alliance is a

relevant predictor of outcome in mental health interventions (Kazdin 2007). Still, modern research on the effects of psychedelic therapy hasn't fully embarked on the delicate task of better understanding the role of the therapist/guide in influencing the outcomes of the psychedelic experience (Carhart-Harris, Goodwin 2017). Other factors that have been hypothesized to enhance treatment efficacy are expectancy (Kirsch 2013) and suggestibility (Carhart-Harris *et al.* 2015).

Current suggestions and guidelines highlight the importance of building rapport, promoting mental openness, “letting go” of resistance, reliance on the unconscious and integration sessions (Johnson, Richards, Griffiths 2008; Richards 2015; Roseman, Nutt, Carhart-Harris 2017). Emphasis is placed on the non-directive character of the interaction (Roseman, Nutt, Carhart-Harris 2017) and on the collection of patients' personal information in order to provide uninterrupted introspection, better understanding of their experiences and prevent adverse psychological reactions (Johnson, Richards, Griffiths 2008). While this conservative approach is obviously rooted in the need to guarantee the psychological safety of patients/participants and to proceed gradually by isolating variables as much as possible, a more structured approach to therapy may be desirable in the future. These results, together with the horizon of evidence coming from psychedelic research, have led some authors to formulate the concept of *transformation-based psychiatry* (TBP; Scheidegger 2021). This concept is proposed as the evolution from the idea that psychopathology is only caused by deficiencies of neurotransmitters that cause cognitive, emotional and behavioral symptoms and that may be treated by increasing their levels (Nutt 2008). TBP posits that psychological illness «follows from misguided bio-psycho-social processes that await transformation» and that therapy should proceed by identifying the dysfunctional mental states, setting intentions towards change, providing effective psychological interventions during the psychedelic experience and offering integration psychotherapy to consolidate the results and manage potential relapses (Scheidegger 2021).

5. Conclusions

Psychedelic research is a new field that is providing insights in several areas of cognitive science. New evidence indicates that psychedelic compounds may be precious to learn more on states of consciousness, to open to new models of brain and mind functioning and effective therapeutic strategies of the most individually and socially burdensome psychiatric conditions. However, to ensure the growth of this field rigorous methodological strategies must be adopted to compensate for the inherent vulnerabilities of experiments making use of psychedelic compounds.

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