OPINION

# The neurobiology of psychedelic drugs: implications for the treatment of mood disorders

*Franz X. Vollenweider and Michael Kometer*

Abstract | After a pause of nearly 40 years in research into the effects of psychedelic drugs, recent advances in our understanding of the neurobiology of psychedelics, such as lysergic acid diethylamide (LSD), psilocybin and ketamine have led to renewed interest in the clinical potential of psychedelics in the treatment of various psychiatric disorders. Recent behavioural and neuroimaging data show that psychedelics modulate neural circuits that have been implicated in mood and affective disorders, and can reduce the clinical symptoms of these disorders. These findings raise the possibility that research into psychedelics might identify novel therapeutic mechanisms and approaches that are based on glutamate-driven neuroplasticity.

Psychedelic drugs have long held a special fascination for mankind because they produce an altered state of consciousness that is characterized by distortions of perception, hallucinations or visions, ecstasy, dissolution of self boundaries and the experience of union with the world. As plant-derived materials, they have been used traditionally by many indigenous cultures in medical and religious practices for centuries, if not millennia[1].

However, research into psychedelics did not begin until the 1950s after the breakthrough discovery of the classical hallucinogen lysergic acid diethylamide (LSD) by Albert Hofmann[2] (TIMELINE). The classical hallucinogens include indoleamines, such as psilocybin and LSD, and phenethylamines, such as mescaline and 2,5-dimethoxy-4-iodo-amphetamine (DOI). Research into psychedelics was advanced in the mid 1960s by the finding that dissociative anaesthetics such as ketamine and phencyclidine (PCP) also produce psychedelic-like effects[3] (BOX 1). Given their overlapping psychological effects, both classes of drugs are included here as psychedelics.

Depending on the individual taking the drug, their expectations, the setting in which the drug is taken and the drug dose, psychedelics produce a wide range of experiential states, from feelings of boundlessness, unity and bliss on the one hand, to the anxiety-inducing experiences of loss of ego-control and panic on the other hand[4–7]. Researchers from different theoretical disciplines and experimental perspectives have emphasized different experiential states. One emphasis has been placed on the LSD-induced perceptual distortions — including illusions and hallucinations, thought disorder and experiences of split ego[7,8] — that are also seen in naturally occurring psychoses[9–11]. This perspective has prompted the use of psychedelics as research tools for unravelling the neuronal basis of psychotic disorders, such as schizophrenia spectrum disorder. The most recent work has provided compelling evidence that classical hallucinogens primarily act as agonists of serotonin (5-hydroxytryptamine) 2A ($5\text{-HT}_{2A}$) receptors[12] and mimic mainly the so-called positive symptoms (hallucinations and thought disorder) of schizophrenia[10]. Dissociative anaesthetics mimic the positive and the negative symptoms (social withdrawal and apathy) of schizophrenia through antagonism at NMDA (*N*-methyl-D-aspartate) glutamate receptors[13,14].

Emphasis has also been placed on the early observation that LSD can enhance self-awareness and facilitate the recollection of, and release from, emotionally loaded memories[15,16]. This perspective appealed to psychiatrists as a unique property that could facilitate the psychodynamic process during psychotherapy. In fact, by 1965 there were more than 1,000 published clinical studies that reported promising therapeutic effects in over 40,000 subjects[17]. LSD, psilocybin and, sporadically, ketamine have been reported to have therapeutic effects in patients with anxiety and obsessive–compulsive disorders (OCD), depression, sexual dysfunction and alcohol addiction, and to relieve pain and anxiety in patients with terminal cancer[18–23] (BOX 2). Unfortunately, throughout the 1960s and 1970s LSD and related drugs became increasingly associated with cultural rebellion; they were widely popularized as drugs of abuse and were depicted in the media as highly dangerous. Consequently, by about 1970, LSD and related drugs were placed in Schedule I in many western countries. Accordingly, research on the effects of classical psychedelics in humans was severely restricted, funding became difficult and interests in the therapeutic use of these drugs faded, leaving many avenues of inquiry unexplored and many questions unanswered.

With the development of sophisticated neuroimaging and brain-mapping techniques and with the increasing understanding of the molecular mechanisms of action of psychedelics in animals, renewed interest in basic and clinical research with psychedelics in humans has steadily increased since the 1990s. In this Perspective, we review early and current findings of the therapeutic effects of psychedelics and their mechanisms of action in relation to modern concepts of the neurobiology of psychiatric disorders. We then evaluate the extent to which psychedelics may be useful in therapy — aside from their established application as models of psychosis[3,11].

### Current therapeutic studies

Several preclinical studies in the 1990s revealed an important role for the NMDA glutamate receptor in the mechanism of action of antidepressants. These findings consequently gave rise to the hypothesis that the NMDA-antagonist ketamine might have potential as an antidepressant[24]. This hypothesis was validated in an initial double-blind placebo-controlled clinical study in seven medication-free patients with major depression. Specifically, a significant reduction in depression scores on the Hamilton depression rating scale (HDRS) was observed 3 hours after a single infusion of ketamine (0.5 mg per kg), and this effect was sustained for at least 72 hours[25]. Several studies have since replicated this rapid antidepressant effect of ketamine using larger sample sizes and treatment-resistant patients with depression[26–30]. Given that 71% of the patients met response criteria (defined as a 50% reduction in HDRS scores from baseline) within 24 hours[26], this rapid effect has a high therapeutic value. In particular, patients with depression who are suicidal might benefit from such a rapid and marked effect as their acute mortality risk is not considerably diminished with conventional antidepressants owing to their long delay in onset of action (usually 2–3 weeks). Indeed, suicidal ideations were reduced 24 hours after a single ketamine infusion[28].

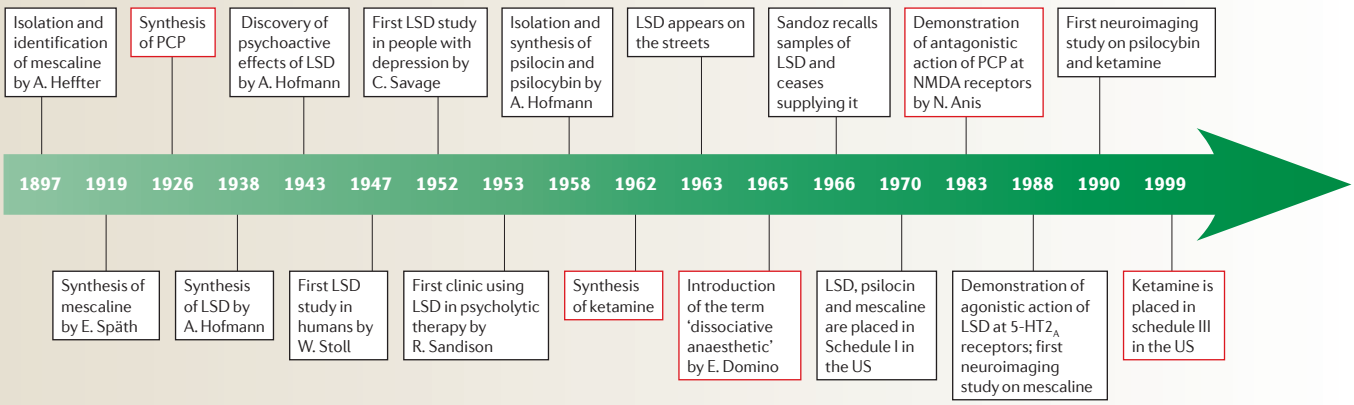
However, despite these impressive and rapid effects, all but 2 of the patients relapsed within 2 weeks after a single dose of ketamine[26]. Previous relapse prevention strategies, such as the administration of either five additional ketamine infusions[29] or riluzole (Rilutek; Sanofi-aventis) on a daily basis[30], yielded success only in some patients and other strategies should be tested in further studies. Moreover, the use of biomarkers that are rooted in psychopathology, neuropsychology and/or genetics might help to predict whether ketamine therapy will be appropriate for a given patient with depression[31]. In line with this idea, decreased activation of the anterior cingulate cortex (ACC) during a working memory task[32] and increased activation of the ACC during an emotional facial processing task[33], as well as a positive family history of alcohol abuse[27], were associated with a stronger antidepressant response to ketamine.

Ketamine therapy could be extended to other disorders in which NMDA receptors are implicated in the pathophysiology — for example, bipolar disorder[34] and addiction[35]. The use of ketamine for the treatment of bipolar disorder is currently being tested (Clinicaltrials.gov: NCT00947791). Its potential as a treatment for addiction is supported by results from a double-blind, randomized clinical trial in which 90 heroin addicts received either existentially oriented psychotherapy in combination with a high dose (2.0 mg per kg) or a low dose of ketamine (0.2 mg per kg). Follow-up studies in the first 2 years revealed a higher rate of abstinence, greater and longer-lasting reductions in craving, and a positive change in nonverbal, unconscious emotional attitude in subjects who had been treated with a high dose, compared with a low dose, of ketamine[36].

In contrast to the rapidly increasing number of clinical studies with ketamine, studies with classic hallucinogens are emerging slowly. This slow progress may be due to the fact that classic hallucinogens are placed in Schedule 1 and therefore have higher regulatory hurdles to overcome and may have negative connotations as a drug of abuse.

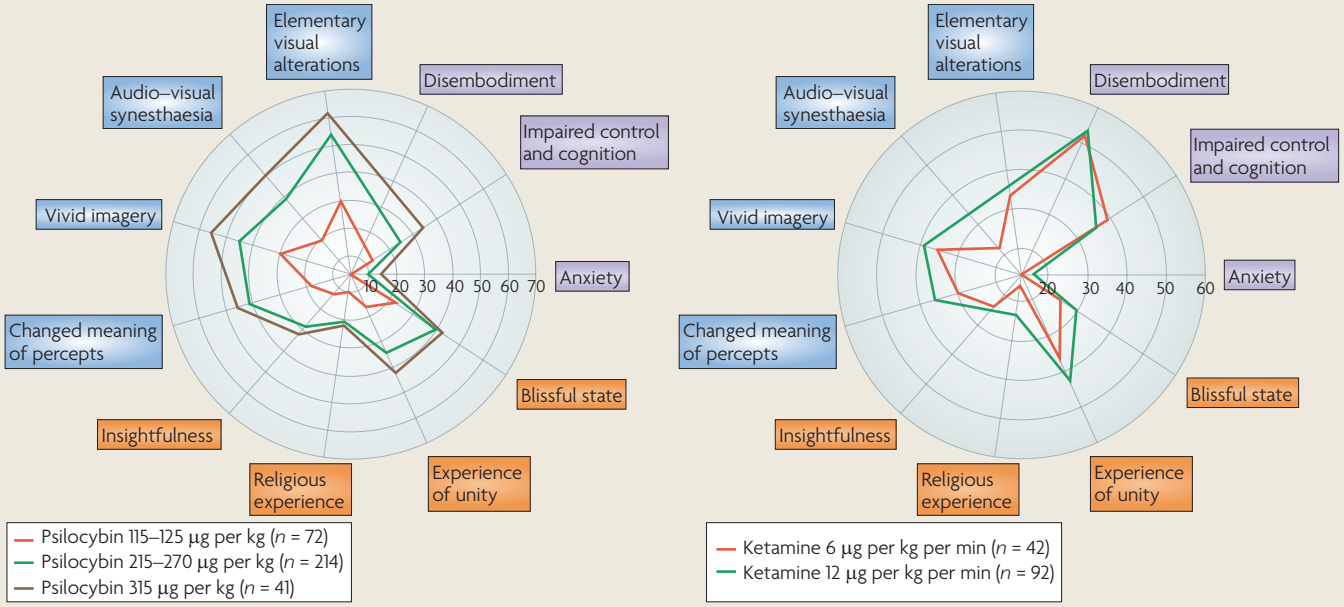
A recent study by Moreno and colleagues[37] evaluated case reports and findings from studies performed in the 1960s that indicated that psilocybin and LSD are effective in the treatment of OCD[22,38–40]. They subsequently carried out a study showing that psilocybin given on four different occasions at escalating doses (ranging from sub-hallucinogenic to hallucinogenic doses) markedly decreased OCD symptoms (by 23–100%) on the Yale–Brown obsessive compulsive scale in patients with OCD who were previously treatment resistant[37]. The reduction in symptoms occurred rapidly, at about 2 h after the peak psychedelic effects, and endured up to the 24-h post-treatment rating[37]. This symptom relief was not related to the dose of the psychedelic drug or to the intensity of the psychedelic experience, and extended beyond the observed acute psychological effect of 4–6 h, raising intriguing questions regarding the mechanisms that underlie this protracted effect[37]. Further research on how this initial relief of symptoms in response to psilocybin — and the subsequent return of symptoms — is linked to functional changes in the brain could contribute not only to a mechanistic explanation of the potentially beneficial effects of psychedelics but also to the development of novel treatments for OCD. The chronicity and disease burden of OCD, the suboptimal nature of available treatments and the observation that psilocybin was well tolerated in OCD patients are clear indications that further studies into the duration, efficacy and

Timeline | **A brief history of psychedelic drugs**




LSD, lysergic acid diethylamide; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine. Discoveries relating to classical hallucinogens and to dissociative anaesthetics are shown by black and red boxes, respectively.

Box 1 | **Assessing altered states of consciousness**




Quantifying altered states of consciousness was problematic in the early years of hallucinogen research. Today, however, there are validated instruments for assessing various aspects of consciousness. According to Dittrich[133], hallucinogen-induced altered states of consciousness can be reliably measured by the five-dimensional altered states of consciousness (5DASC) rating scale. This scale comprises five primary dimensions and their respective subdimensions (see the figure). The primary dimensions are 'oceanic boundlessness' (shown by orange boxes), referring to positively experienced loss of ego boundaries that are associated with changes in the sense of time and emotions — ranging from heightened mood to sublime happiness and feelings of unity with the environment; 'anxious ego-disintegration' (shown by purple boxes), including thought disorder and loss of self-control; 'visionary restructuralization' (shown by blue boxes), referring to perceptual alterations (such as visual illusions and hallucinations), and altered meaning of percepts; acoustic alterations (not shown), including hypersensitivity to sound and auditory hallucinations; and altered vigilance (not shown).

In general, the intensity of these psychedelic-induced alterations of consciousness and perception is dose-dependent, so that hallucinations that involve disorientation in person, place and time rarely, if ever, occur with low to medium doses[4–6]. However, at larger doses — and depending on the individual, his or her expectations and the setting — the same hallucinogen might produce a pleasurable loss of ego boundaries combined with feelings of oneness or might lead to a more psychotic ego dissolution that involves fear and paranoid ideation[4,132,134]. Such experiential phenomena are otherwise rarely reported except in dreams, contemplative or religious exaltation and acute psychoses[11,135]. The figure shows that the classical hallucinogen psilocybin (0.015–0.027 g per kg, by mouth) (see the figure, left) and the dissociative s-ketamine (6–12 µg per kg per min, intravenously) (see the figure, right) produce a set of overlapping psychological experiences, measured by the 5DASC rating scale and respective subscales. The scales indicate the percentage scored of the maximum score.

mechanisms of action of psilocybin or of related compounds in the treatment of OCD are warranted.

Encouraged by early findings (BOX 2), several clinical centres have begun to investigate the potential beneficial effects of psilocybin (ClinicalTrials.gov: NCT00302744, NCT00957359 and NCT00465595) and LSD (ClinicalTrials.gov: NCT00920387) in the treatment of anxiety and depression in patients with terminal cancer, using state of the art, double-blind, placebo-controlled designs. One of these studies has recently been completed and revealed that moderate doses of psilocybin improved mood and reduced anxiety and that this relief variably lasted between 2 weeks and 6 months in patients with advanced cancer (C.S. Grob, personal communication). Finally, another recent study reported that psilocybin and LSD aborted attacks, terminated the cluster period or extended the remission period in people suffering from cluster headaches[41]. Taken together, these findings support early observations in the 1960s that classical hallucinogens have antinociceptive potential and may not only reduce symptoms but also induce long-lasting adaptive processes.

## Neurobiology of psychedelic drugs

The enormous progress that has been made in our understanding of the mechanisms of action of psychedelics[12,42–45] and the neurobiology of affective disorders[34,46,47] has enabled us to postulate new hypotheses regarding the therapeutic mechanisms of psychedelics and their clinical applications. Here we focus on the glutamatergic and serotonergic mechanisms of action of psychedelics with regard to their most promising indications — that is, their use in the treatment of depression and anxiety.

***Classical hallucinogens.*** The classical hallucinogens are comprised of three main chemical classes: the plant-derived tryptamines (for example, psilocybin) and phenethylamines (for example, mescaline), and the semisynthetic ergolines (for example, LSD)[48]. Although all classical hallucinogens display high affinity for 5-$HT_2$ receptors, they also interact to some degree with 5-$HT_1$, 5-$HT_4$, 5-$HT_5$, 5-$HT_6$ and 5-$HT_7$ receptors[12]. In contrast to the tryptamines, the ergolines also show high intrinsic activity at dopamine D2 receptors and at α-adrenergic receptors[49].

Converging evidence from pharmacological[50], electrophysiological[51,52] and behavioural studies in animals[53,54] suggests that classical hallucinogens produce their effects in animals and possibly in humans primarily through agonistic actions at cortical 5-$HT_{2A}$ receptors (FIG. 1a). Consistent with this view, selectively restoring 5-$HT_{2A}$ receptors in

cortical pyramidal neurons is sufficient to rescue hallucinogen-induced head shaking in transgenic mice that lack 5-$HT_{2A}$ receptors[53,55]. Importantly, administration of the 5-$HT_{2A}$ receptor antagonist ketanserin abolishes virtually all of the psilocybin-induced subjective effects in humans[56]. Recent studies have demonstrated that hallucinogenic and non-hallucinogenic 5-$HT_{2A}$ agonists differentially regulate intracellular signalling pathways in cortical pyramidal neurons and that this results in a differential expression of downstream signalling proteins, such as early growth response protein 1 (EGR1), EGR2 and β-arrestin 2[55,57]. This suggests that further elucidation of hallucinogen-specific signalling pathways may aid the development of functionally selective ligands with specific therapeutic properties — for example, ligands that have antidepressant effects but no hallucinogenic effects.

Several studies have demonstrated that activation of 5-$HT_{2A}$ receptors by classical hallucinogens or by serotonin leads to a robust, glutamate-dependent increase in the activity of pyramidal neurons, preferentially those in layer V of the prefrontal cortex (PFC)[51,52,58,59] (FIG. 1a). This increase in glutamatergic synaptic activity was initially thought to result from stimulation of presynaptic 5-$HT_{2A}$ receptors located on glutamatergic thalamocortical afferents to the PFC[60,61]. However, more recent studies suggest that stimulation of postsynaptic 5-$HT_{2A}$ receptors[55,58,59] on a subpopulation of pyramidal cells in the deep layers of the PFC[59] leads to an increase in glutamatergic recurrent network activity[59,62]. The increase in glutamatergic synaptic activity can be abolished not only by specific 5-$HT_{2A}$ antagonists but also by AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid) receptor antagonists[63], by agonists[51] and positive allosteric modulators of metabotropic glutamate receptor 2 (mGluR2)[64], and by selective antagonists of the NR2B subunit of NMDA receptors[65]. Taken together, these findings indicate that classical hallucinogens are potent modulators of prefrontal network activity that involves a complex interaction between the serotonin and glutamate systems in prefrontal circuits.

Activation of 5-$HT_{2A}$ and 5-$HT_{1A}$ receptors in the medial PFC (mPFC) also has downstream effects on serotonergic and dopaminergic activity through descending projections to the dorsal raphe and the ventral tegmental area (VTA). For example, activation of 5-$HT_{2A}$ receptors in the mPFC increases the firing rate of 5-HT neurons in the dorsal raphe and of dopamine neurons in the VTA, resulting in an increased release of 5-HT in the mPFC[58,66] and of dopamine in mesocortical areas[67] in animals. In a study in humans, the hallucinogenic 5-$HT_{2A}$ agonist psilocybin increased striatal dopamine concentrations, and this increase correlated with euphoria and depersonalization phenomena[68]. Blocking dopamine D2 receptors by haloperidol, however, reduced these effects by only about 30%. This suggests that the dopaminergic system contributes only moderately to the broad spectrum of psilocybin-induced psychological alterations[56].

Interestingly, 5-$HT_{2A}$ receptor activation not only seems to underlie the preponderance of the acute psychedelic effects of hallucinogens but may also lead to neuroplastic adaptations in an extended prefrontal–limbic network. For example, in rats a single dose of the hallucinogen DOI transiently increased the dendritic spine size in cortical neurons[69] and repeated doses of LSD downregulated cortical 5-$HT_{2A}$ but not 5-$HT_{1A}$ receptors; effects that were the most pronounced in the frontomedial cortex and ACC[70,71]. It is possible that such adaptations — and specifically a downregulation of prefrontal 5-$HT_{2A}$ receptors — might underlie some of the therapeutic effects of hallucinogens in the treatment of depression, anxiety and chronic pain. In favour of this hypothesis, 5-$HT_{2A}$ receptor density was found to be increased in the PFC in post-mortem samples[72] and *in vivo*[73,74] in patients with major depression, and to be reduced after chronic treatment with various antidepressants — the reduction coinciding with the onset of clinical efficacy[75–77]. In addition, chronic, antisense-mediated downregulation of 5-$HT_{2A}$ receptors in rats[78] and in 5-$HT_{2A}$ knockout mice[79] reduced anxiety-like behaviour, and selective restoration of 5-$HT_{2A}$ receptors in the PFC normalized anxiety-like behaviour in these 5-$HT_{2A}$ knockout mice. These findings suggest that prefrontal 5-$HT_{2A}$ receptors might modulate the activity of subcortical structures, such as the amygdala[79]. Anxiety and depression are interrelated with stress[80], which also affects the serotonin system[81]. Stress elevates corticotropin-releasing factor (CRF)[82], and administration of CRF into the mPFC of mice enhanced anxiety-like

Box 2 | **Early therapeutic findings with psychedelics**

By 1953, two forms of lysergic acid diethylamide (LSD) therapy based on different theoretical frameworks were emerging. These have been named psychedelic (mind-manifesting)[136] and psycholytic (psyche-loosening)[15] therapies. In psychedelic therapy, which was practised mostly in North America, a large dose of LSD (200–800 μg) was applied in a single session. This was thought to induce an overwhelming and supposedly conversion-like peak experience that would bring the subject to a new level of awareness and self-knowledge. It was thought that that this would facilitate self-actualization and lead to permanent changes that would be beneficial to the subject[128,129]. Furthermore, it was claimed that intensive psychotherapeutic preparation of the patient before the drug session and a follow-up integration of the peak experience in further drug-free sessions were crucial for an optimal outcome[130]. Promising therapeutic effects of this therapy were found in people with terminal cancer[20,137], in severe alcoholics[138,139], in people who were addicted to narcotics[140] and in patients with neurosis[141]. For example, a series of studies showed that LSD could reduce depression and decrease apprehension towards death and, surprisingly, that LSD had transient analgesic effects that were superior to those of dihydromorphinone (also known as hydromorphone and Palladone SR (Napp)) and meperidine (also known as pethidine)[20]. These effects were confirmed in later studies and the clinical efficacy was linked with the intensity of the psychedelic experience[129,141,142].

Psycholytic therapy was introduced by Ronald Sandison and applied in Europe at 18 treatment centres[143]. In psycholytic therapy, low to moderate doses of LSD (50–100 μg), psilocybin (10–15 mg) or, sporadically, ketamine were used repeatedly as an adjunct in psychoanalytically oriented psychotherapy to accelerate the therapeutic process by facilitating regression and the recollection and release of emotionally loaded repressed memories, and by increasing the transference reaction[15,22,144–147]. A review of 42 studies reported impressive improvement rates in (mostly treatment-resistant) patients with anxiety disorders (improvement in 70% of patients), depression (in 62% of patients), personality disorders (in 53–61% of patients), sexual dysfunction (in 50% of patients) and obsessive–compulsive disorders (in 42% of patients)[148].

Unfortunately, the majority of these studies had serious methodological flaws by contemporary standards. In particular, with the absence of adequate control groups and follow-up measurements and with vague criteria for therapeutic outcome, the studies did not clearly establish whether it was the drug or the therapeutic engagement that produced the reported beneficial effect. It was also difficult to draw firm conclusions regarding potential long-term efficacy. Nevertheless, the studies provide a conceptual framework for the application of psychedelics, with the data suggesting that the most promising indication for psychedelic use might be found in the treatment of depression and anxiety disorders.

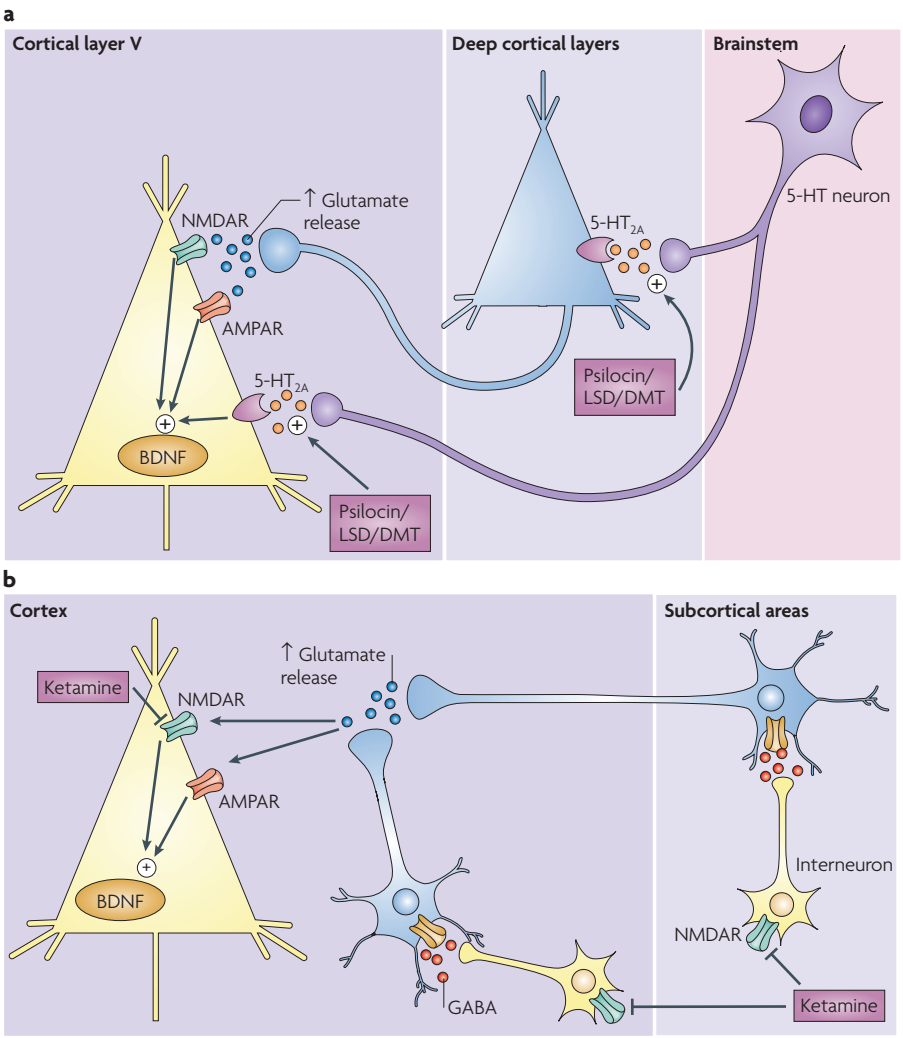



Figure 1 | **Activation of the prefrontal network and glutamate release by psychedelics. a** | The figure shows a model in which hallucinogens, such as psilocin, lysergic acid diethylamide (LSD) and dimethyltryptamine (DMT), increase extracellular glutamate levels in the prefrontal cortex through stimulation of postsynaptic serotonin (5-hydroxytryptamine) 2A (5-$HT_{2A}$) receptors that are located on large glutamatergic pyramidal cells in deep cortical layers (V and VI) projecting to layer V pyramidal neurons. This glutamate release leads to an activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (*N*-methyl-D-aspartate) receptors on cortical pyramidal neurons. In addition, hallucinogens directly activate 5-$HT_{2A}$ receptors located on cortical pyramidal neurons. This activation is thought to ultimately lead to increased expression of brain-derived neurotrophic factor (BDNF). **b** | The figure shows a model in which dissociative NMDA antagonists, such as ketamine, block inhibitory GABA (γ-aminobutyric acid)-ergic interneurons in cortical and subcortical brain areas, leading to enhanced firing of glutamatergic projection neurons and increased extracellular glutamate levels in the prefrontal cortex. As ketamine also blocks NMDA receptors on cortical pyramidal neurons, the increased glutamate release in the cortex is thought to stimulate cortical AMPA more than NMDA receptors. The increased AMPA-receptor-mediated throughput relative to NMDA-receptor-mediated throughput is thought ultimately to lead to increased expression of BDNF.

behaviour in response to DOI through sensitization of 5-$HT_2$ receptor signalling in the PFC[83]. In humans, fronto-limbic 5-$HT_{2A}$ receptor density is correlated not only with anxiety but also with an individual's difficulties in coping with stress[84]. Indeed, recent studies showed that prefrontal 5-$HT_{2A}$ receptors located on descending projections that control serotonergic activity in the dorsal raphe are involved in stress responses[67,85]. Together, these findings suggest that down-regulation of prefrontal 5-$HT_{2A}$ receptors by classical hallucinogens might underlie some of the effects of hallucinogens on depression and anxiety.

Finally, with regard to the finding that LSD reduces anxiety and pain in cancer patients[20], it is of note that prefrontal 5-$HT_{2A}$ density correlated with responses to tonic pain but not with responses to short phasic pain stimuli. This suggests a role of the 5-$HT_{2A}$ receptors in the cognitive evaluation of pain experiences[86] and points to additional therapeutic potential for hallucinogens in individuals with chronic pain.

***Dissociative anaesthetics.*** At sub-anaesthetic doses, dissociative anaesthetics, such as ketamine, primarily block the NMDA receptor at the PCP binding site in the receptor's ionotropic channel[14] (FIG. 1b). The psychoactive potency of the S-ketamine enantiomer is three to four times higher than that of the R-ketamine enantiomer. This is paralleled by their relative affinities at the NMDA receptor complex[87]. Systemic administration of non-competitive NMDA antagonists, such as ketamine, PCP and MK-801 (also known as dizocilpine), in rats markedly increases glutamate release in the mPFC[88,89] concomitant with an increase in the firing rate of pyramidal neurons in this area[90]. These effects are probably due to a blockade of NMDA receptors on GABA (γ-aminobutyric acid)-ergic interneurons[45,91] in cortical and/or subcortical structures and to the subsequent reduction of inhibitory control over prefrontal glutamatergic neurons[92]. The increased extracellular glutamate levels in the mPFC seem to contribute to the psychotropic effects of ketamine and PCP, as AMPA receptor antagonists[88] or agonists of mGluR2 and mGluR3 (REF. 93) abolished various behavioural effects of NMDA antagonists in rats. Likewise, the behavioural effects of selective NR2B antagonists — such as CP-101,606 (also known as Traxoprodil), which produces dose-dependent psychotropic effects similar to those of ketamine in humans[94] — can be blocked by administration of AMPA receptor antagonists[95]. Finally, lamotrigine, which reduces presynaptic glutamate release, attenuated the subjective effects of S-ketamine in humans[96].

In addition to having these glutamatergic effects, non-competitive NMDA receptor antagonists increase extracellular prefrontal and mesolimbic dopamine[89,93] and prefrontal serotonin[89] levels in rats, presumably by stimulating corticofugal glutamate release in the VTA[97] and the dorsal raphe[89], respectively. Studies into the contribution of this dopaminergic and serotonergic activation to the behavioural effects of NMDA antagonists are scant and the results are somewhat controversial. Specifically, in two studies in humans, ketamine-induced striatal dopamine release correlated with the extent of ketamine-induced psychotic

symptoms[98,99], but in another study systemic administration of the dopamine D2 receptor antagonist haloperidol did not attenuate ketamine-induced psychotic symptoms in healthy volunteers[100]. Although 5-$HT_{2A}$ receptor antagonists reverse the disruptive effects of NMDA antagonists on sensorimotor gating[101] and on object recognition[102] in animals, no comparable studies of the role of serotonin in the mechanism of action of NMDA antagonists have been conducted in humans.

The enhanced glutamate release that results from NMDA receptor blockade by ketamine leads to an increased activation of AMPA receptors relative to NMDA receptors[95]. The antidepressant-like effects of ketamine and the selective NR2B antagonist CP-101,606 in animals can be blocked by administration of the AMPA receptor antagonist 2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo[f]quinoxaline-2,3-dione (NBQX)[95], suggesting that enhanced AMPA activation in cortical circuits is crucial for the therapeutic effect of NMDA receptor antagonists[34,95].

***A common mechanism?*** There is accumulating evidence that, despite their different primary modes of action, classical hallucinogens and dissociative anaesthetics both modulate glutamatergic neurotransmission in the prefrontal–limbic circuitry that is implicated in the pathophysiology of mood disorders. This modulation is evidenced by the observation in rats that hallucinogens[103,104] and dissociative anaesthetics[88,89] have a similar effect in enhancing extracellular glutamate release in the PFC, leading to increased activation of pyramidal cells[63,65,105,106]. Furthermore, and congruent with these findings, human neuroimaging studies have shown that both psilocybin and ketamine markedly activate prefrontal cortical areas, including the ACC and insula and, to a lesser extent, temporal and parieto-occipital regions[107–111] (FIG. 2).

According to current models of emotion regulation the PFC, including the ACC, exerts 'cognitive', top-down control over emotion and stress responses through its connections to the amygdala and dorsal raphe[47,85]. Reduced prefrontal glutamate levels that are associated with attenuated PFC activation in response to emotional stimuli[34,112,113] have been reported in patients with depression. Further, depressed individuals[46] and subjects with high trait anxiety[114] show reduced PFC activity when executive control is engaged, and might suffer from decreased top-down inhibition of amygdala activity[115,116]. Conversely, chronic treatment with selective serotonin reuptake inhibitors (SSRIs) increases the functional connectivity between the amygdala and the PFC[117], and attenuates the amygdala response to the presentation of images showing sad faces in patients with depression[118,119]. This suggests that the normalization of this dysregulated network might be important in the recovery from depression[46].

Given that both psilocybin and ketamine increase extracellular glutamate levels in the prefrontal–limbic circuitry in rats and that the antidepressant effects of both drugs outlast their acute psychotropic effects in depressed patients, we propose that a normalization of this network through a glutamate-dependent neuroplastic adaptation is the common therapeutic mechanism of these drugs. Specifically, we posit that psychedelics enhance neuroplasticity by increasing AMPA-type glutamate receptor trafficking and by raising the level of brain-derived neurotropic factor (BDNF). Deficits in these neuroplastic mechanisms have been implicated in the pathophysiology of depression[34,120]. Normalization of these neuroplastic deficits might contribute not only to the relatively sustained antidepressant effects of ketamine[121,122] but also to those of psilocybin. In line with this view, both classes of drugs have been demonstrated to stimulate AMPA receptors by increasing extracellular glutamate levels[6,95] and to increase BDNF levels in prefrontal and limbic brain areas in rats[123–125]. A recent study in patients with depression, however, failed to demonstrate an increase in BDNF plasma levels in the first 4 h after ketamine infusion[122]. Whether ketamine treatment leads to an increase in BDNF levels at a later time and whether such an increase is associated with sustained antidepressant effects warrants further investigation.

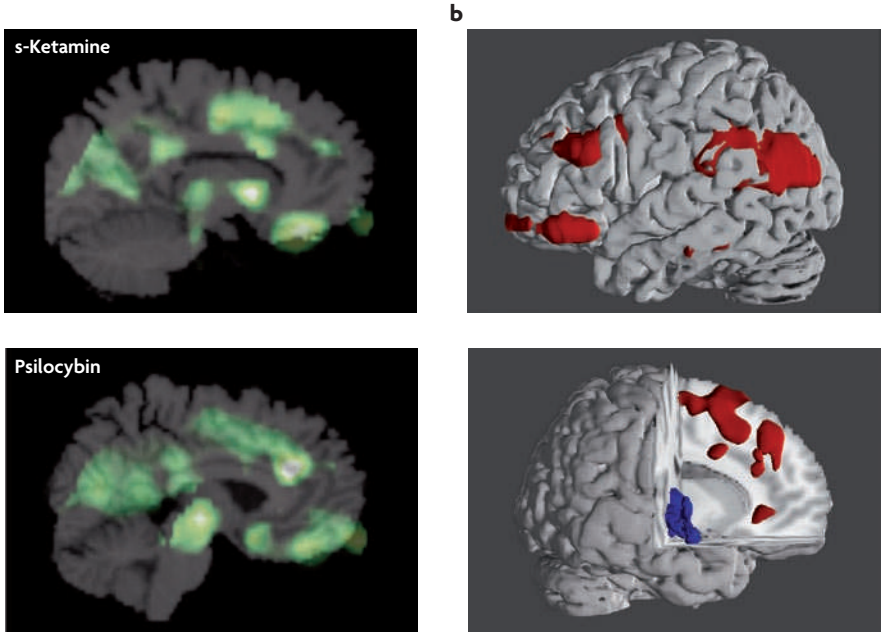



Figure 2 | **Brain activity patterns in psychedelic-induced states of consciousness. a** | Brain imaging studies using $^{18}$fluorodeoxyglucose [$^{18}$FDG] positron emission tomography (PET) revealed that moderate doses of s-ketamine (top) and psilocybin (bottom) in healthy volunteers increased neuronal activity. This is shown by changes in the cerebral metabolic rate for glucose (CMRglu) in the prefrontal cortex and associated limbic regions and in subcortical structures, including the thalamus[107,109]. This similar prefrontal–limbic activation pattern supports the view that both classes of drugs have converging effects on a final pathway or neurotransmitter system. **b** | Recent [$^{18}$FDG] PET brain imaging studies have demonstrated that the degree to which each of the psychedelic-induced key dimensions of altered states of consciousness (BOX 2) is manifested and correlated with functional alterations in cortical and limbic regions and subcortical structures, including the basal ganglia and thalamus. For example, the intensity of experience of the key dimension 'oceanic boundlessness' correlated with the s-ketamine- and psilocybin-induced activation (red) of a prefrontal–parietal network and the deactivation (blue) of a striato–limbic amygdalocentric network[149].

## Conclusions and future directions

The clinical findings and current understanding of the mechanisms of action of classical hallucinogens and dissociative anaesthetics converge on the idea that psychedelics might be useful in the treatment of major depression, anxiety disorders and OCD. These are serious, debilitating, life-shortening illnesses, and as the currently available treatments have high failure rates, psychedelics might offer alternative

treatment strategies that could improve the well-being of patients and the associated economic burden on patients and society.

Accumulating evidence shows a crucial role for the glutamate system in the regulation of neuronal plasticity, and indicates that abnormalities in neuroplasticity contribute to the pathophysiology of mood disorders. Thus, drugs that target neuronal plasticity may offer a novel approach to their treatment. This Perspective proposes that classical psychedelics, such as psilocybin, and dissociative anaesthetics, such as ketamine, alter glutamatergic neurotransmission in prefrontal–limbic circuitries, and that this leads to neuroplastic adaptations, presumably through enhancement of AMPA receptor function. These adaptations may explain some of the shared and relatively sustained antidepressant effects that are observed in clinical studies with ketamine and psilocybin. To further validate this glutamate-induced neuroplasticity hypothesis the relationship between measures of glutamatergic activity and clinical outcome needs to be established. Moreover, the finding that classical hallucinogens (unlike dissociative anaesthetics) also modulate 5-$HT_{2A}$ receptor signalling suggests that they may improve subtypes of anxiety and stress-related disorders. Studies that use biomarkers for genotypes or that use expression levels of 5-$HT_{2A}$ receptors in parallel with clinical end points would be essential not only for clarifying the role of 5-$HT_{2A}$ receptors in the therapeutic mechanism of classical hallucinogens but also for the development of personalized medicines in the treatment of anxiety and stress-related disorders.

In addition, to optimize the clinical benefits of psychedelics and to reduce their unwanted side effects, a deeper understanding of various factors is necessary. These include structure–activity relationships, dose–response relationships and the influence of psychotherapeutic approaches on the effects of psychedelics. In this context, it is interesting to note that there was no indication of prolonged psychosis, persisting perception disorder or subsequent drug abuse after psilocybin[126] or ketamine[127] administration in a large sample of psychotherapeutically well-prepared healthy subjects in a supportive research setting. Similar observations were reported in small samples of patients with depression[29] and OCD[37]. Nonetheless, it is often claimed that the dissociative effects of, for example, ketamine may limit clinical use, despite its reported efficacy[24,94]. In this sense, understanding the molecular mechanism of action could inform the development of novel ligands for 5-$HT_{2A}$ or NMDA receptors that display antidepressant properties but have fewer dissociative effects than psilocybin and ketamine. Further evaluations of the dose–response relationship may be another approach to minimize unwanted side effects. For example, low to moderate oral doses of psilocybin (<0.215 mg per kg) were found to only rarely produce anxious dissociative symptoms in controlled settings[126] (BOX 1) but to reduce anxiety, depression and OCD symptoms in patients[22,37]. Similarly, a low dose of the NR2B antagonist CP-101,606 (in combination with an SSRI) had transient antidepressant effects in a small sample of patients with depression and only rarely induced dissociative symptoms[94].

To take the opposite perspective, it is noteworthy that initial clinical applications of psychedelics in psychedelic and psycholytic therapy were based on the premise that the drug-induced psychological experience had an essential, facilitatory effect on the psychotherapeutic process — that is, it was a form of pharmacology-assisted psychotherapy. Indeed, it has been shown that the transcendent peak (mystical-type) experience, which has a key role in the therapeutic outcome in psychedelic therapy[128–130] and was rated as among the most personally meaningful experiences[131,132], occurs in most cases only in supportive settings and after high-dose administration of psychedelics. One might interpret this concept as an early example of the neuroplasticity hypothesis in which the drug-induced experience and its integration in the psychotherapeutic process is the crucial mechanism that enables neuroplasticity and behavioural changes. By contrast, current pharmacological strategies often assume that medication alone produces neuroplastic adaptations. However, drugs that increase neuroplasticity, such as psychedelics, might be particularly clinically efficient in combination with psychotherapeutic interventions[121]. In support of this notion, cognitive behavioural therapy was shown to normalize prefrontal–limbic functioning in depressed patients[46], and could therefore enhance the proposed neuroplastic effects of psychedelics in prefrontal–limbic structures as discussed here. Thus, further blind, controlled studies are obviously now needed to test these alternative and opposing hypotheses.

The potential of drugs to target glutamatergic neurotransmission in prefrontal–limbic circuitries and to facilitate neuroplastic adaptations may translate into promising new treatment approaches for affective disorders. The novel hypotheses presented here now need to be investigated using well-controlled clinical studies, keeping in mind the controversial history of this class of drugs.

## Glossary

**Cluster period**
A period of time during which cluster headache attacks occur regularly.

**Enantiomers**
Two stereoisomeric molecules that are mirror images of each other and are not superimposable.

**Existentially oriented psychotherapy**
A form of therapy that emphasizes the development of a sense of self-direction through choice and of awareness in resolving existential conflicts (such as the inevitability of death, isolation and meaninglessness).

**Neurosis**
A former term for a category of mental disorders characterized by anxiety and a sense of distress. This category includes disorders now classified as mood disorders, anxiety disorders, dissociative disorders, sexual disorders and somatoform disorders.

**Psychoanalytically oriented psychotherapy**
A therapy based on Freudian psychoanalysis in which unconscious conflicts that are thought to cause the patient's symptoms are brought into consciousness to create insight for the resolution of the problems.

**Regression**
In Freudian psychoanalytic theory this term describes a psychological strategy to cope with reality by means of a temporary reversion of the ego to an earlier stage of development.

**Riluzole**
A drug used to treat amyotrophic lateral sclerosis and that has NMDA (*N*-methyl-D-aspartate) receptor blocking properties similar to those of ketamine.

**Schedule 1**
A legislative category containing controlled drugs that have a high potential for abuse, a lack of accepted safety and no currently accepted medical use in treatments.

**Selective serotonin reuptake inhibitors**
A class of compounds typically used as antidepressants.

**Self-actualization**
The motivation to realize all of one's potential.

**Structure–activity relationship**
(Often abbreviated to SAR.) This is the relationship between the chemical structure of a molecule and its biological activity.

**Transference**
A phenomenon in psychoanalysis characterized by unconscious redirection of feelings or desires from one person to another.

*Franz X. Vollenweider and Michael Kometer are at the Neuropsychopharmacology and Brain Imaging Research Unit, University Hospital of Psychiatry, Zurich, Switzerland.*

*Franz X. Vollenweider is also at the School of Medicine, University of Zurich, Switzerland.*

*Correspondence to F.X.V.*
*e-mail: vollen@bli.uzh.ch*

doi:10.1038/nrn2884
Published online 18 August 2010

1. Hofmann, A. & Schultes, R. E. *Plants of the Gods* (McGraw-Hill Book Company, Maidenhead, UK, 1979).
2. Hofmann, A. in *Chemical Constitution and Pharmacodynamic Actions* (ed. Burger, A.) 169–235 (M.Dekker, New York, 1968).
3. Domino, E. F., Kamenka, J. M. & Gneste, P. The joint French–US seminar on phencyclidine and related arylcyclohexylamines. *Trends Pharmacol. Sci.* **9**, 363–367 (1983).
4. Hasler, F., Grimberg, U., Benz, M. A., Huber, T. & Vollenweider, F. X. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology* **172**, 145–156 (2004).
5. Dittrich, A. in *50 Years of LSD. Current Status and Perspectives of Hallucinogens* (eds Pletscher, A. & Ladewig, D.) 101–118 (Parthenon, New York, 1994).
6. Fischer, R., Marks, P. A., Hill, R. M. & Rockey, M. A. Personality structure as the main determinant of drug induced (model) psychoses. *Nature* **218**, 296–298 (1968).
7. Leuner, H. *Die Experimentelle Psychose* (Springer, Berlin Göttingen Heidelberg, 1962).
8. Hoch, P. H., Cattell, J. P. & Pennes, H. H. Effects of mescaline and lysergic acid (d-LSD-25). *Am. J. Psychiatry* **108**, 579–584 (1952).
9. Chapman, J. The early symptoms of schizophrenia. *Br. J. Psychiatry* **112**, 225–251 (1966).
10. Gouzoulis-Mayfrank, E. *et al.* Hallucinogenic drug induced states resemble acute endogenous psychoses: results of an empirical study. *Eur. Psychiatry* **13**, 399–406 (1998).
11. Geyer, M. A. & Vollenweider, F. X. Serotonin research: contributions to understanding psychoses. *Trends Pharmacol. Sci.* **29**, 445–453 (2008).
12. Nichols, D. E. Hallucinogens. *Pharmacol. Ther.* **101**, 131–181 (2004).
13. Krystal, J. H. *et al.* Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. *Arch. Gen. Psychiatry* **51**, 199–214 (1994).
14. Anis, N. A., Berry, S. C., Burton, N. R. & Lodge, D. The dissociative anesthetics, ketamine and phencyclidine selective reduce excitation of central mammalian neurons by *N*-methyl-D-aspartate. *Br. J. Pharmacol.* **79**, 565–575 (1983).
15. Sandison, R. A. Psychological aspects of the LSD treatment of neuroses. *J. Ment Sci.* **100**, 508–515 (1954).
16. Schmiege, G. R. Jr. LSD as a therapeutic tool. *J. Med. Soc. N.J.* **60**, 203–207 (1963).
17. Malleson, N. Acute adverse reactions to LSD in clinical and experimental use in the United Kingdom. *Br. J. Psychiatry* **118**, 229–230 (1971).
18. Hoffer, A. in *The Uses and Implications of Hallucinogenic Drugs* (eds Aaronson, B. & Osmond, H.) 357–366 (Hogarth Press, London, 1970).
19. Abramson, H. *The use of LSD in Psychotherapy and Alcoholism* (Bobbs-Merrill, New York, 1967).
20. Kast, E. in *LSD: The Consciousness Expanding Drug* (ed. Solomon, D.) 241–256 (G.P. Putman, New York, 1964).
21. Pahnke, W. N., Kurland, A. A., Goodman, L. E. & Richards, W. A. LSD-assisted psychotherapy with terminal cancer patients. *Curr. Psychiatr. Ther.* **9**, 144–152 (1969).
22. Leuner, H. in *50 Years of LSD: Current Status and Perspectives of Hallucinogen Research* (eds Pletscher, A. & Ladewig, D.) 175–189 (Parthenon, New York, 1994).
23. Kurland, A. A., Unger, S., Shaffer, J. W. & Savage, C. Psychedelic therapy utilizing LSD in the treatment of the alcoholic patient: a preliminary report. *Am. J. Psychiatry* **123**, 1202–1209 (1967).
24. Skolnick, P., Popik, P. & Trullas, R. Glutamate-based antidepressants: 20 years on. *Trends Pharmacol. Sci.* **30**, 563–569 (2009).
25. Berman, R. M. *et al.* Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* **47**, 351–354 (2000).
26. Zarate, C. A. Jr *et al.* A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry* **63**, 856–864 (2006).
27. Phelps, L. E. *et al.* Family history of alcohol dependence and initial antidepressant response to an *N*-methyl-D-aspartate antagonist. *Biol. Psychiatry* **65**, 181–184 (2009).
28. Price, R. B., Nock, M. K., Charney, D. S. & Mathew, S. J. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol. Psychiatry* **66**, 522–526 (2009).
29. Aan het Rot, M. *et al.* Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol. Psychiatry* **67**, 139–145 (2010).
30. Mathew, S. J. et *al.* Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. *Int. J. Neuropsychopharmacol.* **13**, 71–82 (2010).
31. Holsboer, F. How can we realize the promise of personalized antidepressant medicines? *Nature Rev. Neurosci.* **9**, 638–646 (2008).
32. Salvadore, G. *et al.* Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. *Neuropsychopharmacology* **35**, 1415–1422 (2010).
33. Salvadore, G. *et al.* Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. *Biol. Psychiatry* **65**, 289–295 (2009).
34. Sanacora, G., Zarate, C. A., Krystal, J. H. & Manji, H. K. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nature Rev. Drug Discov.* **7**, 426–437 (2008).
35. Lau, C. G. & Zukin, R. S. NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. *Nature Rev. Neurosci.* **8**, 413–426 (2007).
36. Krupitsky, E. *et al.* Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up. *J. Subst. Abuse Treatment* **23**, 273–283 (2002).
37. Moreno, F. A., Wiegand, C. B., Taitano, E. K. & Delgado, P. L. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J. Clin. Psychiatry* **67**, 1735–1740 (2006).
38. Brandrup, E. & Vanggaard, T. LSD treatment in a severe case of compulsive neurosis. *Acta Psychiatr. Scand.* **55**, 127–141 (1977).
39. Leonard, H. L. & Rapoport, J. L. Relief of obsessive–compulsive symptoms by LSD and psilocin. *Am. J. Psychiatry* **144**, 1239–1240 (1987).
40. Moreno, F. A. & Delgado, P. L. Hallucinogen-induced relief of obsessions and compulsions. *Am. J. Psychiatry* **154**, 1037–1038 (1997).
41. Sewell, R. A., Halpern, J. H. & Pope, H. G. Jr. Response of cluster headache to psilocybin and LSD. *Neurology* **66**, 1920–1922 (2006).
42. Gonzalez-Maeso, J. & Sealfon, S. C. Agonist-trafficking and hallucinogens. *Curr. Med. Chem.* **16**, 1017–1027 (2009).
43. Winter, J. C. Hallucinogens as discriminative stimuli in animals: LSD, phenethylamines, and tryptamines. *Psychopharmacology (Berlin)* **203**, 251–263 (2009).
44. Large, C. H. Do NMDA receptor antagonist models of schizophrenia predict the clinical efficacy of antipsychotic drugs? *J. Psychopharmacol.* **21**, 283–301 (2007).
45. Quirk, M. C., Sosulski, D. L., Feierstein, C. E., Uchida, N. & Mainen, Z. F. A defined network of fast-spiking interneurons in orbitofrontal cortex: responses to behavioral contingencies and ketamine administration. *Front. Syst. Neurosci.* **3**, 13 (2009).
46. DeRubeis, R. J., Siegle, G. J. & Hollon, S. D. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nature Rev. Neurosci.* **9**, 788–796 (2008).
47. Clark, L., Chamberlain, S. R. & Sahakian, B. J. Neurocognitive mechanisms in depression: implications for treatment. *Annu. Rev. Neurosci.* **32**, 57–74 (2009).
48. Geyer, M. A., Nichols, D. E. & Vollenweider, F. X. in *Encyclopedia of Neuroscience* (ed. Squire, L. R.) 741–748 (Academic Press, Oxford, 2009).
49. Marona-Lewicka, D., Thisted, R. A. & Nichols, D. E. Distinct temporal phases in the behavioral pharmacology of LSD: dopamine D2 receptor-mediated effects in the rat and implications for psychosis. *Psychopharmacologia (Berlin)* **180**, 427–435 (2005).
50. Glennon, R. A., Titeler, M. & McKenney, J. D. Evidence for 5-HT2 involvement in the mechanism of action of hallucinogenic agents. *Life Sci.* **35**, 2505–2511 (1984).
51. Aghajanian, G. K. & Marek, G. J. Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. *Neuropsychopharmacology* **36**, 589–599 (1997).
52. Aghajanian, G. K. & Marek, G. J. Serotonin, via 5-HT2A receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. *Brain Res.* **825**, 161–171 (1999).
53. Wing, L. L., Tapson, G. S. & Geyer, M. A. 5HT-2 mediation of acute behavioral effects of hallucinogens in rats. *Psychopharmacology* **100**, 417–425 (1990).
54. Sipes, T. E. & Geyer, M. A. DOI disruption of prepulse inhibition of startle in the rat is mediated by 5-HT2A and not by 5-HT2C receptors. *Behav. Pharmacol.* **6**, 839–842 (1995).
55. Gonzalez-Maeso, J. *et al.* Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* **53**, 439–452 (2007).
56. Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F. I., Bäbler, A., Vogel, H. & Hell, D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* **9**, 3897–3902 (1998).
57. Schmid, C. L., Raehal, K. M. & Bohn, L. M. Agonist-directed signaling of the serotonin 2A receptor depends on β-arrestin-2 interactions *in vivo*. *Proc. Natl Acad. Sci. USA* **105**, 1079–1084 (2008).
58. Puig, M. V., Celada, P., az-Mataix, L. & Artigas, F. *In vivo* modulation of the activity of pyramidal neurons in the rat medial prefrontal cortex by 5-HT2A receptors: relationship to thalamocortical afferents. *Cereb. Cortex* **13**, 870–882 (2003).
59. Beique, J. C., Imad, M., Mladenovic, L., Gingrich, J. A. & Andrade, R. Mechanism of the 5-hydroxytryptamine 2A receptor-mediated facilitation of synaptic activity in prefrontal cortex. *Proc. Natl Acad. Sci. USA* **104**, 9870–9875 (2007).
60. Aghajanian, G. K. & Marek, G. J. Serotonin and hallucinogens. *Neuropsychopharmacology* **21**, 16S–23S (1999).
61. Marek, G. J., Wright, R. A., Gewirtz, J. C. & Schoepp, D. D. A major role for thalamocortical afferents in serotonergic hallucinogen receptor function in the rat neocortex. *Neuroscience* **105**, 379–392 (2001).
62. Aghajanian, G. K. Modeling 'psychosis' *in vitro* by inducing disordered neuronal network activity in cortical brain slices. *Psychopharmacology (Berlin)* **206**, 575–585 (2009).
63. Zhang, C. & Marek, G. J. AMPA receptor involvement in 5-hydroxytryptamine2A receptor-mediated prefrontal cortical excitatory synaptic currents and DOI-induced head shakes. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **32**, 62–71 (2008).
64. Benneyworth, M. A. *et al.* A selective positive allosteric modulator of metabotropic glutamate receptor subtype 2 blocks a hallucinogenic drug model of psychosis. *Mol. Pharmacol.* **72**, 477–484 (2007).
65. Lambe, E. K. & Aghajanian, G. K. Hallucinogen-induced UP states in the brain slice of rat prefrontal cortex: role of glutamate spillover and NR2B-NMDA receptors. *Neuropsychopharmacology* **31**, 1682–1689 (2006).
66. Celada, P., Puig, M. V., Casanovas, J. M., Guillazo, G. & Artigas, F. Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: Involvement of serotonin-1A, GABA(A), and glutamate receptors. *J. Neurosci.* **21**, 9917–9929 (2001).
67. Vazquez-Borsetti, P., Cortes, R. & Artigas, F. Pyramidal neurons in rat prefrontal cortex projecting to ventral tegmental area and dorsal raphe nucleus express 5-HT2A receptors. *Cereb. Cortex* **19**, 1678–1686 (2009).
68. Vollenweider, F. X., Vontobel, P., Hell, D. & Leenders, K. L. 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man: A PET study with [11C]raclopride. *Neuropsychopharmacology* **20**, 424–433 (1999).
69. Jones, K. A. *et al.* Rapid modulation of spine morphology by the 5-HT2A serotonin receptor through kalirin-7 signaling. *Proc. Natl Acad. Sci. USA* **106**, 19575–19580 (2009).
70. Buckholtz, N. S., Zhou, D. F., Freedman, D. X. & Potter, W. Z. Lysergic acid diethylamide (LSD) administration selectively downregulates serotonin2 receptors in rat brain. *Neuropsychopharmacology* **3**, 137–148 (1990).
71. Gresch, P. J., Smith, R. L., Barrett, R. J. & Sanders-Bush, E. Behavioral tolerance to lysergic acid diethylamide is associated with reduced serotonin-2A receptor signaling in rat cortex. *Neuropsychopharmacology* **30**, 1693–1702 (2005).

72. Shelton, R. C., Sanders-Bush, E., Manier, D. H. & Lewis, D. A. Elevated 5-HT 2A receptors in postmortem prefrontal cortex in major depression is associated with reduced activity of protein kinase, A. *Neuroscience* **158**, 1406–1415 (2008).
73. Bhagwagar, Z. *et al.* Increased 5-$HT_{2A}$ receptor binding in euthymic, medication-free patients recovered from depression: a positron emission study with [$^{11}$C]MDL 100,907. *Am. J. Psychiatry* **163**, 1580–1587 (2006).
74. Meyer, J. H. *et al.* Dysfunctional attitudes and 5-HT2 receptors during depression and self-harm. *Am. J. Psychiatry* **160**, 90–99 (2003).
75. Sibille, E. *et al.* Antisense inhibition of 5-hydroxytryptamine2a receptor induces an antidepressant-like effect in mice. *Mol. Pharmacol.* **52**, 1056–1063 (1997).
76. Yamauchi, M., Miyara, T., Matsushima, T. & Imanishi, T. Desensitization of 5-HT2A receptor function by chronic administration of selective serotonin reuptake inhibitors. *Brain Res.* **1067**, 164–169 (2006).
77. Gomez-Gil, E. *et al.* Decrease of the platelet 5-HT2A receptor function by long-term imipramine treatment in endogenous depression. *Hum. Psychopharmacol.* **19**, 251–258 (2004).
78. Cohen, H. Anxiolytic effect and memory improvement in rats by antisense oligodeoxynucleotide to 5-hydroxytryptamine-2A precursor protein. *Depress. Anxiety.* **22**, 84–93 (2005).
79. Weisstaub, N. V. *et al.* Cortical 5-HT2A receptor signaling modulates anxiety-like behaviors in mice. *Science* **313**, 536–540 (2006).
80. Anisman, H., Merali, Z. & Stead, J. D. Experiential and genetic contributions to depressive- and anxiety-like disorders: clinical and experimental studies. *Neurosci. Biobehav. Rev.* **32**, 1185–1206 (2008).
81. Lukkes, J., Vuong, S., Scholl, J., Oliver, H. & Forster, G. Corticotropin-releasing factor receptor antagonism within the dorsal raphe nucleus reduces social anxiety-like behavior after early-life social isolation. *J. Neurosci.* **29**, 9955–9960 (2009).
82. Reul, J. M. & Holsboer, F. Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. *Curr. Opin. Pharmacol.* **2**, 23–33 (2002).
83. Magalhaes, A. C. *et al.* CRF receptor 1 regulates anxiety behavior via sensitization of 5-HT2 receptor signaling. *Nature Neurosci.* **13**, 622–629 (2010).
84. Frokjaer, V. G. *et al.* Frontolimbic serotonin 2A receptor binding in healthy subjects is associated with personality risk factors for affective disorder. *Biol. Psychiatry* **63**, 569–576 (2008).
85. Amat, J. *et al.* Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nature Neurosci.* **8**, 365–371 (2005).
86. Kupers, R. *et al.* A PET [18F]altanserin study of 5-HT12A receptor binding in the human brain and responses to painful heat stimulation. *Neuroimage* **44**, 1001–1007 (2009).
87. Oye, I., Paulsen, O. & Maurset, A. Effects of ketamine on sensory perception: Evidence for a role of *N*-methyl-D-aspartate receptors. *J. Pharmac. Exp. Ther.* **260**, 1209–1213 (1992).
88. Moghaddam, B., Adams, B., Verma, A. & Daly, D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J. Neurosci.* **17**, 2921–2927 (1997).
89. Lopez-Gil, X. *et al.* Clozapine and haloperidol differently suppress the MK-801-increased glutamatergic and serotonergic transmission in the medial prefrontal cortex of the rat. *Neuropsychopharmacology* **32**, 2087–2097 (2007).
90. Jackson, M. E., Homayoun, H. & Moghaddam, B. NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex. *Proc. Natl Acad. Sci. USA* **101**, 8467–8472 (2004).
91. Homayoun, H. & Moghaddam, B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J. Neurosci.* **27**, 11496–11500 (2007).
92. Jodo, E. *et al.* Activation of medial prefrontal cortex by phencyclidine is mediated via a hippocampo-prefrontal pathway. *Cereb. Cortex* **15**, 663–669 (2005).
93. Moghaddam, B. & Adams, B. W. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. *Science* **281**, 1349–1352 (1998).
94. Preskorn, S. H. *et al.* An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective *N*-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J. Clin. Psychopharmacol.* **28**, 631–637 (2008).
95. Maeng, S. *et al.* Cellular mechanisms underlying the antidepressant effects of ketamine: role of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol. Psychiatry* **63**, 349–352 (2008).
96. Anand, A. *et al.* Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of *N*-methyl-D-aspartate receptor antagonists. *Arch. Gen. Psychiatry* **57**, 270–276 (2000).
97. Jentsch, J. D., Tran, A., Taylor, J. R. & Roth, R. H. Prefrontal cortical involvement in phencyclidine-induced activation of the mesolimbic dopamine system: behavioral and neurochemical evidence. *Psychopharmacology (Berlin)* **138**, 89–95 (1998).
98. Breier, A. *et al.* Effects of NMDA antagonism on striatal dopamine release in healthy subjects — application of a novel PET approach. *Synapse* **29**, 142–147 (1998).
99. Vollenweider, F. X., Vontobel, P., Leenders, K. L. & Hell, D. Effects of *S*-ketamine on striatal dopamine release: a [11C] raclopride PET study of a model psychosis in humans. *J. Psych. Res.* **34**, 35–43 (2000).
100. Krystal, J. H. *et al.* Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology* **145**, 193–204 (1999).
101. Varty, G. B., Bakshi, V. P. & Geyer, M. A. M100907, a serotonin 5-$HT_{2A}$ receptor antagonist and putative antipsychotic, blocks dizocilpine-induced prepulse inhibition deficits in sprague-dawley and wistar rats. *Neuropsychopharmacology* **20**, 311–321 (1999).
102. Snigdha, S. *et al.* Attenuation of phencyclidine-induced object recognition deficits by the combination of atypical antipsychotic drugs and pimavanserin (ACP 103), a 5-hydroxytryptamine(2A) receptor inverse agonist. *J. Pharmacol. Exp. Ther.* **332**, 622–631 (2010).
103. Scruggs, J. L., Schmidt, D. & Deutch, A. Y. The hallucinogen 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI) increases cortical extracellular glutamate levels in rats. *Neurosci. Lett.* **346**, 137–140 (2003).
104. Muschamp, J. W., Regina, M. J., Hull, E. M., Winter, J. C. & Rabin, R. A. Lysergic acid diethylamide and [-]-2,5-dimethoxy-4-methylamphetamine increase extracellular glutamate in rat prefrontal cortex. *Brain Res.* **1023**, 134–140 (2004).
105. Kargieman, L., Santana, N., Mengod, G., Celada, P. & Artigas, F. Antipsychotic drugs reverse the disruption in prefrontal cortex function produced by NMDA receptor blockade with phencyclidine. *Proc. Natl Acad. Sci. USA* **104**, 14843–14848 (2007).
106. Shi, W. X. & Zhang, X. X. Dendritic glutamate-induced bursting in the prefrontal cortex: further characterization and effects of phencyclidine. *J. Pharmacol. Exp. Ther.* **305**, 680–687 (2003).
107. Vollenweider, F. X. *et al.* Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [F-18]-fluorodeoxyglucose (FDG). *Eur. Neuropsychopharmacol.* **7**, 9–24 (1997).
108. Vollenweider, F. X. *et al.* Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology* **16**, 357–372 (1997).
109. Vollenweider, F. X., Leenders, K. L., Oye, I., Hell, D. & Angst, J. Differential psychopathology and patterns of cerebral glucose utilisation produced by (*S*)- and (*R*)-ketamine in healthy volunteers measured by FDG-PET. *Eur. Neuropsychopharmacol.* **7**, 25–38 (1997).
110. Schreckenberger, M. *et al.* The psilocybin psychosis as a model psychosis paradigma for acute schizophrenia: a PET study with 18-FDG. *Eur. J. Nucl. Med.* **25**, 877 (1998).
111. Gouzoulis-Mayfrank, E. *et al.* Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and D-methamphetamine in healthy volunteers. A double-blind, placebo-controlled PET study with [18F]FDG. *Neuropsychopharmacology* **20**, 565–581 (1999).
112. Walter, M. *et al.* The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. *Arch. Gen. Psychiatry* **66**, 478–486 (2009).
113. Hasler, G. *et al.* Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch. Gen. Psychiatry* **64**, 193–200 (2007).
114. Bishop, S. J. Trait anxiety and impoverished prefrontal control of attention. *Nature Neurosci.* **12**, 92–98 (2009).
115. Bishop, S. J. Neural mechanisms underlying selective attention to threat. *Ann. NY Acad. Sci.* **1129**, 141–152 (2008).
116. Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H. & Davidson, R. J. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J. Neurosci.* **27**, 8877–8884 (2007).
117. Chen, C. H. *et al.* Functional coupling of the amygdala in depressed patients treated with antidepressant medication. *Neuropsychopharmacology* **33**, 1909–1918 (2008).
118. Fu, C. H. *et al.* Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch. Gen. Psychiatry* **61**, 877–889 (2004).
119. Sheline, Y. I. *et al.* Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol. Psychiatry* **50**, 651–658 (2001).
120. Martinowich, K., Manji, H. & Lu, B. New insights into BDNF function in depression and anxiety. *Nature Neurosci.* **10**, 1089–1093 (2007).
121. Krystal, J. H. *et al.* Neuroplasticity as a target for the pharmacotherapy of anxiety disorders, mood disorders, and schizophrenia. *Drug Discov. Today* **14**, 690–697 (2009).
122. Machado-Vieira, R., Salvadore, G., DiazGranados, N. & Zarate, C. A. Jr. Ketamine and the next generation of antidepressants with a rapid onset of action. *Pharmacol. Ther.* **123**, 143–150 (2009).
123. Vaidya, V. A., Marek, G. J., Aghajanian, G. K. & Duman, R. S. 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. *J. Neurosci.* **17**, 2785–2795 (1997).
124. Cavus, I. & Duman, R. S. Influence of estradiol, stress, and 5-HT2A agonist treatment on brain-derived neurotrophic factor expression in female rats. *Biol. Psychiatry* **54**, 59–69 (2003).
125. Garcia, L. S. *et al.* Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **33**, 450–455 (2009).
126. Studerus, E., Kometer, M., Hasler, F. & Vollenweider, F. X. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. *J. Psychopharmacology* (in the press).
127. Perry, E. B. Jr *et al.* Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology (Berlin)* **192**, 253–260 (2007).
128. Savage, C., Savage, E., Fadiman, J. & Harman, W. W. LSD: Therapeutic effects of the psychedelic experience. *Psychol. Rep.* **14**, 111–120 (1964).
129. Pahnke, W. N., Kurland, A. A., Unger, S., Savage, C. & Grof, S. The experimental use of psychedelic (LSD) psychotherapy. *JAMA* **212**, 1856–1863 (1970).
130. Kurland, A. A., Grof, S. & Panke, W. N. G. L. E. LSD in the treatment of alcoholics. *Pharmakopsychiatr. Neuropsychopharmakol.* **4**, 83–94 (1971).
131. Griffiths, R. R., Richards, W., Johnson, M., McCann, U. & Jesse, R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J. Psychopharmacol.* **22**, 621–632 (2008).
132. Griffiths, R. R., Richards, W. A., McCann, U. & Jesse, R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berlin)* **187**, 268–283 (2006).
133. Dittrich, A. The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. *Pharmacopsychiatry* **31**, 80–84 (1998).
134. Vollenweider, F. X. Advances and pathophysiological models of hallucinogen drug actions in humans: a preamble to schizophrenia research. *Pharmacopsychiatry* **31**, 92–103 (1998).
135. Fischer, R. A cartography of the ecstatic and meditative states. *Science* **174**, 897–904 (1971).

136. Osmond, H. A review of the clinical effects of psychotomimetic agents. *Ann. NY Acad. Sci.* **66**, 418–434 (1957).
137. Kurland, A. A. LSD in the supportive care of the terminally ill cancer patient. *J. Psychoactive Drugs* **17**, 279–290 (1985).
138. Abramson, H. A. *The Use of LSD in Psychotherapy and Alcoholism* (Bobbs-Merrill, Indianapolis, 1967).
139. Hollister, L. E., Shelton, J. & Krieger, G. A controlled comparison of lysergic acid diethylamide (LSD) and dextroamphetmine in alcoholics. *Am. J. Psychiatry* **125**, 1352–1357 (1969).
140. Savage, C. & McCabe, O. L. Residential psychedelic (LSD) therapy for the narcotic addict. A controlled study. *Arch. Gen. Psychiatry* **28**, 808–814 (1973).
141. Grof, S., Goodman, L. E., Richards, W. A. & Kurland, A. A. LSD-assisted psychotherapy in patients with terminal cancer. *Int. Pharmacopsychiatry* **8**, 129–144 (1973).
142. Pahnke, W. N. Psychedelic drugs and mystical experience. *Int. Psychiatry Clin.* **5**, 149–162 (1969).
143. Grinspoon, L. & Bakalar, J. B. *Psychedelic Drugs Reconsidered* (Basic Books., New York, 1979).
144. Crocket, R., Sandison, R. A. & Walk, A. in *Proc. R. Med–Psychol. Assoc.* (Lewis & Co., London, 1963).
145. Leuner H. *in Ethnopsychotherapie* (eds Dittrich, A. & Scharfetter, C.) 151–161 (Enke, Stuttgard, 1987)
146. Geert-Jorgensen, E. Further observations regarding hallucinogenic treatment. *Acta Psychiatr. Scand.* **203** (Suppl.), 195–200 (1968).
147. Khorramzadeh, E. & Lotfy, A. O. The use of ketamine in psychiatry. *Psychosomatics* **14**, 344–346 (1973).
148. Mascher, E. in *Neuro-Psychopharmacology* (eds Brill, H., Cole, J. O., Denker, P., Hippins, H. & Bradley, P. B.) 441–444 (Excerpta-Medica, Amsterdam, 2010).
149. Vollenweider, F. X. Brain mechanisms of hallucinogens and entactogens. *Dialogues Clin. Neurosci.* **3**, 265–279 (2001).

**Acknowledgements**
The authors would like to acknowledge the financial support of the Swiss Neuromatrix Foundation (to F.X.V. and M.K.), and of the Heffter Research Institute (to F.X.V.). The authors thank D. Nichols for critical comments on the manuscript.

**Competing interests statement**
The authors declare no competing financial interests.

**DATABASES**
**ClinicalTrials.gov:** http://clinicaltrials.gov
NCT00302744 | NCT00465595 | NCT00920387 | NCT00947791 | NCT00957359
**UniProtKB:** http://www.uniprot.org
β-arrestin 2 | EGR1 | EGR2 | mGluR2 | mGluR3

**FURTHER INFORMATION**
**University of Zurich Neuropsychopharmacology and Brain Imaging Group's homepage:** http://www.dcp.uzh.ch/research/groups/neuropsychopharmacology.html

**ALL LINKS ARE ACTIVE IN THE ONLINE PDF**

SCIENCE AND SOCIETY

# Socioeconomic status and the brain: mechanistic insights from human and animal research

*Daniel A. Hackman, Martha J. Farah and Michael J. Meaney*

Abstract | Human brain development occurs within a socioeconomic context and childhood socioeconomic status (SES) influences neural development — particularly of the systems that subserve language and executive function. Research in humans and in animal models has implicated prenatal factors, parent–child interactions and cognitive stimulation in the home environment in the effects of SES on neural development. These findings provide a unique opportunity for understanding how environmental factors can lead to individual differences in brain development, and for improving the programmes and policies that are designed to alleviate SES-related disparities in mental health and academic achievement.

As the field of human neuroscience has matured, it has progressed from describing the 'typical' or 'average' human brain to characterizing individual differences in brain structure and function, and identifying their determinants. Socioeconomic status (SES), a measure of one's overall status and position in society, strongly influences an individual's experiences from childhood and through adult life. Research is beginning to shed light on the mechanisms through which experiences in the social world during early childhood affect the structure and function of the brain.

Growing up in a family with low SES is associated with substantially worse health and impaired psychological well-being, and impaired cognitive and emotional development throughout the lifespan[1–6]. In contrast to sociological and epidemiological approaches, neuroscience can identify the underlying cognitive and affective systems that are influenced by SES (BOX 1). In addition, neuroscience research — in animals and in humans — has provided candidate mechanisms for the cause–effect relationships between SES and neural development. This research has also demonstrated that at least some of these effects are reversible. Such a mechanistic understanding will enable the design of more specific and powerful interventions to prevent and remediate the effects of low childhood SES[7–9].

Other recent reviews have discussed research on SES-related differences in neurocognitive development[7–9]. In this Perspective, we focus on the candidate mechanisms by which SES influences brain development, drawing from research in humans and in animal models. We first describe studies in humans that show that SES influences cognitive and affective function in children, adolescents and young adults. We then discuss studies in human populations that have identified possible mediators of the effects of SES, and review research in animals in which these factors were directly manipulated to assess their effect on offspring outcomes.

## SES effects on mental health and cognition

SES is a complex construct that is based on household income, material resources, education and occupation, as well as related neighbourhood and family characteristics, such as exposure to violence and toxins, parental care and provision of a cognitively stimulating environment[2,5,10,11] (for controversies regarding the measurement and defining levels of SES see REFS 1,10,11). Not only the lowest stratum but all levels of SES affect emotional and cognitive development to varying degrees[1,12–14]. This implies that the effects of SES that are reviewed here are relevant to the entire population, although it should be noted that the strongest effects are often seen in people with the lowest levels of SES.

Compared with children and adolescents from higher-SES backgrounds, children and adolescents from low-SES backgrounds show higher rates of depression, anxiety, attention problems and conduct disorders[12,15–18], and a higher prevalence of internalizing (that is, depression- or anxiety-like) and externalizing (that is, aggressive and impulsive) behaviours[6,19–21], all of which increase with the duration of impoverishment[12,21]. In addition, childhood SES influences cognitive development; it is positively correlated with intelligence and academic achievement from early childhood and through adolescence[2,3,6,14,19,22,23].