Improving cognitive functioning in major depressive disorder with psychedelics: A dimensional approach

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ABSTRACT

The high symptomatic and biological heterogeneity of major depressive disorder (MDD) makes it very difficult to find broadly efficacious treatments that work against all symptoms. Concentrating on single core symptoms that are biologically well understood might consist of a more viable approach. The Research Domain Criteria (RDoC) framework is a trans-diagnostic dimensional approach that focuses on symptoms and their underlying neurobiology. Evidence is accumulating that psychedelics may possess antidepressant activity, and this can potentially be explained through a multi-level (psychobiological, circuitry, (sub)cellular and molecular) analysis of the cognitive systems RDoC domain. Cognitive deficits, such as negative emotional processing and negativity bias, often lead to depressive rumination. Psychedelics can increase long-term cognitive flexibility, leading to normalization of negativity bias and reduction in rumination. We propose a theoretical model that explains how psychedelics can reduce the negativity bias in depressed patients. At the psychobiological level, we hypothesize that the negativity bias in MDD is due to impaired pattern separation and that psychedelics such as psilocybin help in depression because they enhance pattern separation and hence reduce negativity bias. Pattern separation is a mnemonic process that relies on adult hippocampal neurogenesis, where similar inputs are made more distinct, which is essential for optimal encoding of contextual information. Impairment in this process may underlie the negative cognitive bias in MDD by, for example, increased pattern separation of cues with a negative valence that can lead to excessive deliberation on aversive outcomes. On the (sub) cellular level, psychedelics stimulate hippocampal neurogenesis as well as synaptogenesis, spineogenesis and dendritogenesis in the prefrontal cortex. Together, these effects help restoring resilience to chronic stress and lead to modulation of the major connectivity hubs of the prefrontal cortex, hippocampus, and amygdala. Based on these observations, we propose a new translational framework to guide the development of a novel generation of therapeutics to treat the cognitive symptoms in MDD.

1. Introduction

Major depressive disorder (MDD) is the most common mood disorder according to the World Health Organization (WHO) (Kessler et al., 2009), which has predicted it to be the leading cause of burden of disease worldwide by 2030. Moreover, the current COVID-19 pandemic likely will worsen these prediction, as the virus negatively affects the psychological well-being of the general population in both direct and indirect ways (Ettman, Abdalla, Cohen, Sampson, Vivier, & Galea, 2020; Mazza et al., 2020). A substantial number of patients that are treated with antidepressants does not experience remission and the need for new treatments remains high (Rucker, Jelen, Flynn, Frowde, & Young, 2016). One of the challenges in CNS drug discovery is the diagnosis of mental health disorders based on categorical nosologies: The Diagnostic and Statistical Manual of Mental Disorders (DSM) and the WHO’s International Classification of Diseases (ICD). Both rely on the presence of specific symptoms that are often shared between disorders. However, mental disorders typically consist of a combination of symptoms forming a syndrome that causes functional impairment (Malhi & Mann, 2018). For the diagnosis of MDD, five of nine different symptoms described in the DSM need to be present (Drysdale et al., 2017), including one of two core symptoms: depressed mood or anhedonia. Of the remaining seven DSM symptoms, the neurocognitive symptoms decreased ability to think and indecisiveness, and psychomotor retardation...
are of particular interest for the development of novel antidepressants (Malhi & Mann, 2018). Because, for many patients with MDD, the experienced functional impairment as a result of the disease is due to the disruption of cognitive function related to the disorder (Culpepper, Lam, & McIntyre, 2017).

The prefrontal cortex (PFC), hippocampus and amygdala play important roles in the neural circuitries underlying the impaired cognitive functions observed in mental disorders, such as MDD. In fact, both the hippocampus and the PFC are often reduced in size and activity in MDD patients (Frodi et al., 2010). Post mortem human imaging studies, as well as animal studies, suggest that the atrophy of neurons in these areas, as observed by the loss of dendritic spines, neurites and synapses, play a key role in the pathophysiology of cognitive dysfunctions observed in MDD (Liu et al., 2017). This is in line with the idea that neural cell survival, proliferation and plasticity are essential for various cognitive processes because they maintain and update neural connection in important cognitive circuitries (Price & Duman, 2020). Therefore, MDD patients might profoundly benefit from treatments capable of counteracting neuronal atrophy by promoting neuroplasticity - the brain’s ability to react and adapt to outside stimuli - in the PFC and the hippocampus. (Burke & Barnes, 2006). Yet, as for today, there are currently no compounds that have been approved for this scope. We hypothesize that psychedelics may consist of a novel class of antidepressants that can improve cognitive processes in MDD by reversing impaired neuroplasticity.

Recent clinical trials have shown a high therapeutic potential of serotonergic psychedelics for the treatment of depressive disorders, including treatment-resistant depression and MDD (Carhart-Harris, Bolstridge, et al., 2016; Davis, Barrett, & Griffiths, 2020; Davis, Barrett, May, et al., 2020; Vargas, Luís, Barroso, Gallardo, & Pereira, 2020). Psychedelics are compounds capable of inducing profound states of altered mood and perception in humans (Nichols, 2016). This class of compounds includes lysergic acid diethylamide (LSD), n,n-dimethyltryptamine (DMT), and psilocybin, which act as (non-selective) agonists at the serotonin 2a receptor (5-HT2aR) (Ray, 2010;ollenweider & Kometer, 2010). The 5-HT2aR is widely expressed throughout the cortex (Beliveau et al., 2017), and is the primary mediator of the acute subjective effects of psychedelics on cognition (Madsen et al., 2019; Nichols, 2016; Preller et al., 2017). There is supporting evidence that neuroplasticity might play a major role in mediating the antidepressant effects of psychedelics. Yet, despite some proposed theories, the psychobiological mechanism underlying these effects remains poorly understood.

Our aim is to explore the use of a transdiagnostic, dimensional nosology to inform a more targeted application of psychedelics for the treatment of cognitive deficits, such as those observed in MDD (Fig. 2). Next, we will identify the key molecular, cellular and neuro-functional mechanisms that underlie the persistent therapeutic effects of psychedelics. Our hypothesis is that the antidepressant effects of classical psychedelics, such as LSD and psilocybin, involves an improvement in negative bias and cognitive flexibility by promotion of neuroplasticity, which can be measured by improvements in pattern separation performance (Figs. 1 and 4).

1.1. Neurocognitive domains in depression

The cognitive model of depression was first introduced by Aaron Beck (1963). This model considers internalized cognitive schemas that
Fig. 2. Preliminary evidence supports long-term positive effects of serotonergic psychedelics on symptoms of depression in patients with MDD, treatment-resistant depression, and life-threatening cancer with depression (Carhart-Harris, Bolstridge, et al., 2016; Carhart-Harris et al., 2018; Davis, Barrett, & Griffiths, 2020; Davis, Barrett, May, et al., 2020; Dos Santos et al., 2018; Griffiths et al., 2016). According to the cognitive model of depression, the effects of psychedelics on the DSM-V symptoms of depressed mood and anhedonia can be explained through their beneficial effects on the cognitive anomalies observed in depressive disorders. The RDoC domains that represent these symptoms are the positive valence, negative valence, and cognitive systems, respectively. A multi-level analysis of these domain might inform future studies that aim to elucidate the mechanistic properties of these drugs in depressive disorders. MDD = major depressive disorder.

1.2. Neurotrophic hypothesis for depression

The neural mechanism that seems to underlie the negative bias involves hyperactivity of limbic structures and decreased activity in cognitive control regions that modulate it (Fig. 3). In fact, depression derives from the neuropathological connections between these areas, namely the PFC, the hippocampus, and the amygdala (Dean & Keshavan, 2017). The amygdala has a central role in fear perception and emotional processing, which explains its association with mood and anxiety disorders, including MDD (Phelps, 2006). In MDD, the amygdala shows increased reactivity to negative stimuli that correlates with negative affect (Hamilton et al., 2012; Victor, Furey, Fromm, Öhman, & Drevets, 2010). The PFC is an essential area for top-down inhibition of limbic areas, such as the amygdala. Due to the atrophy of neurons observed in the PFC of patients, this top-down modulation is absent in MDD leading to persistent states of negative affect (Bielau et al., 2013; Hastings, Parsey, Oquendo, Arango, & Mann, 2004). Moreover, PFC-dependent processing of negative emotions comes at a higher metabolic cost in patients with MDD (Disner et al., 2011). Another important brain area that is essential for controlling the activation of the amygdala is the hippocampus. A key function of the hippocampus is the registration of changes in context and the ability to link emotions and external context accordingly (Optiz, 2014). Because emotions are constantly influenced by external context and thus change continuously, when uncoupling of emotions and external stimuli takes place the emotions are no longer influenced or changed by external context and set in a fixed state. This fixed state is determined by the emotional state in which the emotional uncoupling takes place. In the case of MDD, this emotional state would be negative affect. Similarly to the PFC, the hippocampus of MDD patients shows signs of atrophy, including reduced size, activity, and levels of neurotrophic factors (Cole et al., 2016; Nunes et al., 2018; Sheldrick, Camara, Ilieva, Riederer, & Michel, 2017; Frodl et al., 2002). This leads to an inability of MDD patients to react flexibly and appropriately to outside stimuli to adequately match mood and behavior to environmental demands (Price & Duman, 2020; this theme will be addressed again in the next section).

The neurotrophic hypothesis of depression provides a valuable framework to help understand the molecular and cellular mechanisms that underly the abnormalities in structure and activity of the PFC and hippocampus. This hypothesis proposes an important role for a reduced neuroplasticity in these regions in the pathophysiology of the disorder (Duman, Aghajanian, Sanacora, & Krystal, 2016). Neuroplasticity is defined as set of biological processes that are required by the brain to adapt and change depending on the environmental needs (Levy et al., 2018). In MDD, a reduction of neuroplasticity in the PFC and hippocampus is observed as a reduction of dendritic arbors and spine density in pyramidal neurons (Forrest, Parnell, & Penzes, 2018). Moreover, reduction of hippocampal neuroplasticity is also observed by decrease in
the number of newborn neurons in the dentate gyrus (DG), a process which is referred to as neurogenesis (Levy et al., 2018). Although it is most active during early life development, recent evidence shows that neurogenesis occurs also in adulthood and this process seems essential for memory processes such as pattern separation (Kempermann, Song, & Gage, 2015; Denoth-Lippuner & Jessberger, 2021; we will pick up this theme again in the next section). In line with the role of the PFC and the hippocampus in the regulation of amygdala-related functions, the RDoC construct of sustained threat of the negative valence domain proposes a role for decreased arborization in PFC and hippocampal neurons in negative affect.

Brain-derived neurotrophic factor (BDNF) signalling helps explain the relationship between depression and the deficits in neuroplasticity. BDNF is believed to be a prime mediator of neuroplasticity (Banasr, Dwyer, & Duman, 2011; Pittenger & Duman, 2008). By binding with high affinity to the tropomyosin receptor kinase B (TrkB),

Table 1

| DSM-5 symptom | RDoC domain | RDoC construct | Deficits in MDD | Reference(s) |
|---------------|-------------|----------------|----------------|--------------|
| Inability to think and indecisiveness | Cognitive systems | Attention | Reduced sustained and divided attention | McClintock, Husain, Greer, & Cullum, 2010 |
| | | | ‘overgeneralized’ memory caused by deficits in retrospective memory retrieval and impairments in new memory formation | van Vreeswijk & de Wilde, 2004; Zhou et al., 2017; Sumner, Griffith, & Mineka, 2010 |
| | | | Reduced executive function in various domains including inhibition, cognitive flexibility, planning, and set-shifting | Dotson et al., 2020 |
| | | | Reduced flexible updating of information and inference control | Joormann & Gotlib, 2008, |

Fig. 3. Simplified diagram of the circuitry of depression and its interactions with stress. Negative emotions activate the amygdala which in turn activates the HPA – axis and therefore causes stress. Stress reactivates the amygdala through glucocorticoids. Chronic stress creates a positive feedback loop favoring negative emotions and releasing more glucocorticoids, which lead to cell death in the hippocampus and the PFC, and therefore reduced function of these areas. In turn, these regions would lose their ability to regulate amygdala reactivity to negative stimuli, which might lead to disinhibition and increase negative affect. HPA = hypothalamic–pituitary–adrenal.
activation of BDNF signalling is an essential requirement for hippocampal neurogenesis and for the processes of neurotrophic, spine- and synaptogenesis and the strengthening of LTP (Cobar, Yuan, & Tashiro, 2017; Phillips, 2017). A reduction of BDNF expression is present in the PFC and hippocampus of MDD patients whereas the opposite is true for the amygdala (Leite et al., 2018; Nunes et al., 2018; Qiao, An, Xu, & Ma, 2017; Sheldrick et al., 2017; Yu & Chen, 2011). Yet, the lower BDNF protein levels and altered epigenetic regulation observed in the blood of MDD patients suggest an overall net reduction of its signalling (Kurita, Nishino, Kato, Numata, & Sato, 2012; Molenjdi et al., 2011, 2014; Van den Berg et al., 2020).

Chronic stress plays an important role in mediating these effects. In fact, chronic stress leads to the steady activation of the hypothalamic–pituitary–adrenal (HPA) axis, which hormones are known to affect BDNF signalling. For example, the increase in glucocorticoid levels induced by chronic stress have been linked to reduced BDNF gene expression in MDD (Kumugi, Hori, Adachi, & Numakawa, 2010). In line with this observation, rodent chronic stress models have shown decreased dendritic arborization and spine density in pyramidal neurons of both the PFC and hippocampus and reduced hippocampal neurogenesis (Banaar et al., 2011). Yet, they also show overexpression of BDNF in the basolateral amygdala of rats (Lakshminarasimhan & Chattarji, 2012), which explains the increase in spine density and excitability of amygdalar neurons observed in these same models (Rosenkranz, Venheim, & Padival, 2010). Because of its stimulatory effects on the HPA axis, the sensitization of the amygdala creates a feed-forward mechanism for the stress response therefore leading to a steady inhibition of cortical and hippocampal neuroplasticity (Herman, McLaveen, Solomon, Carvalho-Netto, & Myers, 2012). Taken together, these observations strongly support the fundamental role that stress, BDNF, and neuroplasticity in the PFC, hippocampus, and the amygdala play in the pathophysiology of depression, according to the cognitive model of Beck (Duman et al., 2016; Fig. 3). Yet, how the changes in BDNF signalling translate into the cognitive deficits that are observed in MDD remains unclear.

1.3. A pattern separation-based translational framework

As mentioned before, the hippocampus is involved in affect regulation due to its role in memory formation and the detection of contextual changes. In this regard, adult hippocampal neurogenesis plays a critical role in encoding functions of the hippocampal circuit such pattern separation. In this mnemonic process, similar inputs are made more distinct (Clelland et al., 2009; Sahay et al., 2011) which is essential for optimal encoding of contextual information to ensure that new experiences are stored without overlapping or interfering with those previously encoded. This minimization of interference is important for the formation of new episodic memories. Pattern separation plays also an important role in the regulation of affect (Perera et al., 2013). This is important with regard to the cognitive model of depression. In fact, impaired pattern separation of cues in the environment may underlie the negative cognitive bias seen in MDD by increased pattern completion of strongly encoded averse memories. The negative response bias may also arise from increased pattern separation of cues with a negative valence that can lead to excessive deliberation on averse outcomes (Nierenberg, 2018). In fact, preliminary evidence suggests that pattern separation of neutral, but not negative items, is impaired in individuals with depressive symptoms (Dery et al., 2013; Shelton & Kirwan, 2013). Moreover, decreased BOLD response in the DG/CA3 region is linked to severity of depressive symptoms and increased ability to discriminate negative scenes (Fujii, Saito, Yanaka, Kosaka, & Okazawa, 2014; Leal, Noche, Murray, & Yassa, 2017). Finally, impaired pattern separation may affect processing of cue contingency relationships and abnormal perception of salience and reward resulting in increased anxiety and anhedonia (Snyder, Soumier, Brewer, Pickel, & Cameron, 2011). Based on this evidence, a role for pattern separation has been proposed in antidepressant action (Sahay & Hen, 2007).

We hypothesize that a tripartite “translational fingerprint” for novel therapeutics that target negativity bias in MDD (Fig. 4). First, an improvement of neuroplasticity, as marked by increases in growth factors such as BDNF; structural changes, such as spinogenesis and synaptogenesis; and an increase in adult newborn cells. Second, these (sub) cellular adaptations would provide the mechanistic basis for improved pattern separation as manifested by restored activity of emotional circuits in the amygdala, hypothalamus, prefrontal cortex and/or nucleus accumbens. And, finally, together, this would lead to a modulation of the expression of fear and stress reactivity, executive functions and anhedonia. Importantly, it is not known whether antidepressants enhance pattern separation in MDD. Although it is encouraging that the SRI vortioxetine increased pattern separation in mice (Felice et al., 2018; unfortunately, a trial in treatment resistant depression (NCT02969876) with pattern separation as an endpoint was put on hold). Relevant in this regard is also that chronic administration of vortioxetine reversed stress-induced cognitive deficits, such as impaired reversal learning and fear memory and extinction, in rodents (Hatherall, Sánchez, & Morilak, 2017; Wallace, Pehmson, Sánchez, & Morilak, 2014). Once a proof of concept has been demonstrated in humans, the path is open for stratification of MDD patients and to predict and monitor treatment responses with pattern separation as a biomarker (Nierenberg, 2018). Moreover, due to its high translational value, pattern separation might serve as solid bridge between preclinical findings and human data, supporting decision making in the drug development process (van Goethem, van Hagen, & Prickaerts, 2018).

What does this “translational fingerprint” look like for psychedelics? We hypothesize that serotonergic psychedelics exert long-term antidepressant effects in MDD by increasing cognitive flexibility and decreasing the negativity bias through stimulation of neuroplasticity mechanisms, and these effects can be observed through a restored pattern separation (Figs. 1 and 4). In the next section, we will show the evidence for the long-term antidepressant effects of acute hallucinogenic doses of the drugs. Subsequently, we will provide an overview of the current knowledge that supports our hypothesis at the behavioural, cognitive, neural, and (sub)cellular level.

1.4. Clinical evidence of the antidepressant effects of psychedelics

During the so-called first wave of psychedelic research, scientists provided initial evidence of the efficacy of psychedelic-assisted psychotherapy at reducing symptoms of depression and anxiety in patients with life-threatening cancer (Grof, Goodman, Richards, & Kurland, 1973; Pahnke et al., 1970). In the last decade, with the start of a second wave, small randomized clinical trials with improved experimental designs were able to replicate these findings in a similar patient population (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). In fact, a meta-analysis of these trials showed a significant reduction in depressive symptoms after single or double administration of hallucinogenic doses of psilocybin, the active compound of hallucinogenic mushrooms, in psychotherapeutic setting (Vargas et al., 2020). Two other studies have further extended these results to other depressive disorders. The first was an open-label study by Carhart-Harris, Bolstridge, et al. (2016) and Carhart-Harris et al. (2018) where the antidepressant effects of a double dose of psilocybin, administered 1 week apart in supportive settings, were observed in a subpopulation of twenty patients with treatment-resistant depression. This study showed long-lasting improvements in depressive symptoms as significant reductions compared to baseline were observed in various psychometric measures of depression and anhedonia during the whole 6-months follow-up period. The second study was a randomized and waiting list-controlled trial conducted by Davis, Barrett, May, et al. (2020) that investigated the effects of two psilocybin sessions in twenty-seven MDD patients. A significant clinical response (>50% reduction in GRID-HAMD score) was found in 67% and 71% of patients at week 1 and 4 post-sesion, respectively. Among these patients, 58% at week 1 and 54% at week 4 showed a GRID-HAMD score
Besides, psychedelics acutely inhibit thalamic gating (or filtering) between these areas (Carhart-Harris, Muthukumaraswamy, et al., 2016). Well-known visual hallucinations, the acute subjective effects of psychedelics include reduction in rigid thinking, enhancement of environmental sensitivity and emotional release (Carhart-Harris, 2015), and reduce the functional connectivity within and between the key areas regarding perception (of the self and of the environment) induced by psychedelics enable a state of unconstrained cognition in which one’s own priory beliefs (of the self and the environment) can be challenged. Therefore, psychedelics offer a psychotherapeutic window in which people can be confronted with negative cognitive schemas.

1.5. The effects of psychedelics on cognitive flexibility

Besides altering the processing of sensory stimuli that leads to the well-known visual hallucinations, the acute subjective effects of psychedelics include reduction in rigid thinking, enhancement of environmental sensitivity and emotional release (Carhart-Harris & Goodwin, 2017; Madsen et al., 2019; Nichols, 2016). Importantly, these effects are believed to be responsible for the long-term antidepressant effects because they allow for the disruption of negative cognitive schemas that are associated with negative affect (Carhart-Harris & Friston, 2019). This can be explained in terms of acute changes in brain connectivity and functional activity following administration of these drugs. In fact, psychedelics affect activity and connectivity of major hubs of default mode network (DMN) that regulates processes of self-referential thinking, autobiographical memory, and reflection of one’s own emotional state (Hamilton, Farmer, Fogelman, & Gotlib, 2015). In line with this functions, increased baseline activity of the DMN has been associated to depressive rumination (Hamilton et al., 2012, 2015). Psychedelics acutely reduce the activity of the brain areas that constitute this network, such as the thalamus, posterior cingulate cortex (PCC), and mPFC (Carhart-Harris, Erritzoe, et al., 2012a; Carhart-Harris, Muthukumaraswamy, et al., 2016; Kometer, Pokorny, Seifritz, & Volleindeiwer, 2015), and reduce the functional connectivity within and between these areas (Carhart-Harris, Muthukumaraswamy, et al., 2016). Besides, psychedelics acutely inhibit thalamic gating (or filtering) of ascending/descending sensory information, as shown by alterations in functional connectivity of this brain area with cortical regions present within the cortico-striato-thalamo-cortical feedback loop (Müller et al., 2017). This results in sensory overload or “flooding” in the cortex, contributing to the effects of psychedelics on hallucinations, cognitive disturbances, and ego dissolution (Vollenweider & Prelier, 2020). Based on this evidence, Carhart-Harris, Leech, et al. (2012) concluded the reduction of connectivity between the brain’s key areas regarding perception (of the self and of the environment) induced by psychedelics enable a state of unconstrained cognition in which one’s own a priori beliefs (of the self and the environment) can be challenged. Therefore, psychedelics offer a psychotherapeutic window in which people can be confronted with negative cognitive schemas, such as those observed in MDD.

Administration of hallucinogenic doses of psychedelics also have long-term beneficial effects on cognitive flexibility, which might be essential for their antidepressant action. In fact, they increased behaviors associated with cognitive flexibility, such as divergent and convergent creative thinking, suggestibility, and openness to new experiences (Carhart-Harris et al., 2015; Carhart-Harris, Bolstridge, et al., 2016; Mason, Mischler, Uthaug, & Kuypers, 2019; Uthaug et al., 2019). For example, a recent study with ayahuasca found an increase in cognitive flexibility, as measured by the Cognitive Flexibility Scale and the Wisconsin Picture Card Sorting Task, the day following administration (Murphy-Beiner & Soar, 2020; Uthaug et al., 2018). Moreover, regular ayahuasca users performed better than non-users in a set shifting task that requires cognitive flexibility (Bouso et al., 2012). With regard to the cognitive model of depression, an increase in cognitive flexibility might exert antidepressant effects by loosening the cognitive biases and therefore a reduction of negative affect present in MDD patients. To support this idea, a study from Davis, Barrett, and Griffiths (2020) revealed a highly significant mediation effect of cognitive flexibility on the association between the acute subjective effects of psychedelics and lower than 7, indicating remission. Similarly, preliminary evidence shows antidepressant properties of other serotonergic psychedelics such as the DMT and LSD (Dos Santos, Osorio, Crippa, & Hallak, 2016; Dos Santos, Osorio, Crippa, Riba, et al., 2016; Dos Santos, Bouso, Alcizar-Córcoles, & Hallak, 2018). Taken together, these results suggest a therapeutic potential for serotonergic psychedelics for the treatment of depressive disorders.

![Fig. 4. A mechanistic framework for the effects of psychedelics on negativity bias in MDD. Psychedelics stimulate neuroplasticity; improve pattern separation, and restore activity of emotional circuits in the amygdala, hypothalamus, prefrontal cortex and/or nucleus accumbens. Together, this leads to a modulation of the expression of fear and stress reactivity, executive functions and anhedonia. Blue: pattern separation-dependent pathway; Green: pattern separation-independent pathway.](image-url)
a post-acute decrease in anxiety and depression. Moreover, Carhart-Harris and colleagues found an association between the long-term antidepressant effects of psilocybin in MDD and changes in resting state functional connectivity (RSFC) between brain areas of the DMN involved in processes of cognitive flexibility, such as attention and memory (Carhart-Harris et al., 2017). In fact, an increase in RSFC between the PFC and the inferior parietal cortex (IPC) and a decrease in RSFC between the parahippocampal region and the PFC induced by psilocybin in patients with treatment-resistant depression were predictive of treatment response on the long-term. According to the RDoC matrix, the IPC is associated with deficits in the working memory subconstruct of active maintenance and limited capacity. In fact, the IPC is believed to mediate attentional allocation in situations where conflicting emotional choices are present (Samara et al., 2018), a process which is required during working memory utilization. In line with this observation, changes in inferior parietal lobule activity have been associated with the reduction in attentional biases by cognitive behavioural therapy in MDD (Samara et al., 2018). The parahippocampus and the PFC are part of the extrinsic hippocampal circuitry, which according to the RDoC is involved in the construct of declarative memory. Studies in patients with mild cognitive impairments showed that increased connectivity between these two areas is positively associated with deficits in semantic memory, such as visual naming (Gardini et al., 2015; Liu et al., 2016). Importantly, improvements in declarative memory have been found after long-term antidepressant treatment and may mediate the therapeutic outcome (Bremmer, Vythilingam, Vermetten, & Charney, 2007). Therefore, it might be interesting to see whether the same applies for psychedelic-assisted psychotherapy in MDD patients.

1.6. The effects of psychedelics on neuroplasticity

The long-term effects of serotonergic psychedelics on cognitive flexibility can be explained by showing their effects in the brain at a cellular and molecular level. Preliminary evidence shows that single doses of psychedelics can induce a long-term stimulation of various mechanisms of neuroplasticity in the PFC and the hippocampus (Fig. 5). In the PFC, an increase in structural and synaptic plasticity is observed after treatment with psychedelics (Barre et al., 2016; Berthoux, Barre, Bockaert, Marin, & Bécamel, 2019; Ly et al., 2018). For example, preclinical studies an increase in neurito-, synapto-, and spino-genesis in frontocortical neurons both in vitro and in vivo (Ly et al., 2018, 2020; Shao et al., 2021, preprint). Moreover, treatment with psilocybin and LSD led to an overexpression of neuroplasticity-related genes in this area (Jeffen, Elving, Wegener, & Müller, 2020; Nichols & Sanders-Bush, 2002). In the hippocampus, on the other hand, the main neuroplastic effect of psychedelics is the promotion of neurogenesis in the DG. In fact, psychedelics increase the number (and dendritic morphological complexity) of newborn DG granule cells in the hippocampus of mice (Catlow, Song, Paredes, Kirstein, & Sanchez-Ramos, 2013; Lima da Cruz, Moulin, Petiz, & Leão, 2018; Morales-Garcia et al., 2020). Importantly, DMT also increased the number of astrocytes and oligodendrocytes and regulated the expansion and differentiation of neuronal stem cells in the DG, both effects suggesting that psychedelics might influence the whole maturation process of newborn neurons (Morales-Garcia et al., 2020).

Although the exact molecular mechanism underlying the effects of psychedelics on neuroplasticity remain poorly understood, BDNF seems to play an important role. In humans, LSD and ayahuasca acutely increased blood BDNF levels (Almeida et al., 2019; Holze et al., 2020). Interestingly, these effects of ayahuasca correlated with a long-term reduction in depressive symptoms in MDD patients (Almeida et al., 2019). The increase in blood BDNF might be explained by looking at the brain-region specific changes in protein level after administration of these drugs in rodents. For example, a study performed in rats showed an increase in hippocampal and cortical BDNF levels after administration of ayahuasca (Colaço et al., 2020). In line with these observations, administration of the 5-HT2A antagonist ketanserin reduced BDNF protein levels in the same area (Jiang et al., 2016; Vaidya, Marek, Aghajanian, & Duman, 1997). Accordingly, administration of the TrKB antagonist ANA-12 or the mTOR antagonist rapamycin blocked the effects of psychedelics on neuroplasticity in primary cortical cell cultures (Ly et al., 2018). Importantly, stimulation of mTOR by psychedelics activated an autoregulatory positive feedback BDNF signaling loop (Ly et al., 2020). This effect might explain the long-term effect of psychedelics on cognitive flexibility that are observed long after the drug has been excreted from the body. Finally, there is evidence to show that psychedelics might also indirectly stimulate neuroplasticity by reducing

![Fig. 5. The effects of psychedelics on cognitive flexibility may involve a long-term increase in neuroplasticity, which is known to be deficient in MDD. In this regard, psychedelics increase synapto-, dendrito-, and neurito-genesis in the PFC and increase the number, maturation, and morphological complexity of neurons in the hippocampus. MDD = major depressive disorder.](image-url)
the activation of the immune system and the HPA-axis in MDD (da Silva et al., 2019; de Menezes Galvão et al., 2018; Galvão-Coelho et al., 2020; Uthaug et al., 2020).

2. Discussion and conclusion

Increasingly, psychedelic medicine research points to potentially valuable, and perhaps previously underappreciated, therapeutic applications, such as the treatment of MDD. A better understanding of their mechanistic action will inform how psychedelics can be best used in clinical practice, as well as help guide the development of a novel generation of psychedelic-like drugs with improved efficacy and side effect profile (“non-hallucinogenic ligands”). Approaching this from a dimensional, RDoC-based perspective, we propose a hypothesis for how psychedelics improve depressive symptoms via a similar mechanism as the antidepressant vortioxetine (Figs. 1 and 4). By stimulating neuroplasticity in the PFC and hippocampus, psychedelics decrease the negativity bias through a restoration of the deficits in pattern separation, leading to a decrease in depressive symptoms. Indeed, Hibicke and Nichols (2020) showed that psilocybin, administered one month before testing, restored the deficits in pattern separation induced by development mental stress in rats and this effect correlated with antidepressant effects in a forced swimming test. Other studies in rodents reported an association between the neuroplastic effects of psychedelics and increased performance in fear extinction and learning and memory tasks (Buchborn, Schröder, Höllt, & Grecksch, 2014; Cameron, Benson, Dunlap, & Olson, 2018; Catlow et al., 2013; Morales-García et al., 2020). Together, these findings are supportive of our hypothesis but clearly more studies are needed to validate our model, as some of the connections between the proposed levels remain insufficiently substantiated (see further).

2.1. Beyond cognition

Our findings can be embedded in a larger dimensional framework than the cognitive system alone. As argued in the section “neurocognitive domains in depression”, the DSM-5 criteria, low mood, anhedonia and ability to think may correspond to the RDoC domains negative valence, positive valence and cognitive systems, respectively (Fig. 2). Multi-level analysis of these domains suggest that psychedelics exert their therapeutic effects in MDD patients by modulating cellular, physiological, and brain activity processes. In line with the cognitive and neurotrophic models of depression, the effects of psychedelics on various constructs of the cognitive systems associated with processes of cognitive flexibility, such as attention, working memory, and declarative memory, might be responsible for a disruption of the negativity bias and a reduction in the deficits in negative and positive affect present in MDD. The latter would be represented by a modulation of various units of analysis included in the constructs of loss and sustained threat of the negative valence domain, and reward anticipation and reward responsiveness in the positive valence domain. Future studies should look into the effects of psychedelic treatment on these domains and their (sub)constructs at various units of analysis, including at the cellular, circuitry, behavioral and self-report level.

2.2. Caveats

Our hypothesized ‘translational fingerprint’ is aimed to provide a heuristic framework for future studies that aim to elucidate the mechanism underlying the antidepressant action of psychedelics. There are several topics that need further consideration.

First, the relationship between drug effects on BDNF and on neuroplasticity processes in the PFC and hippocampus need to be better understood. Are the neuroplastic effects of psychedelics biased towards the PFC compared to the hippocampus? Transcriptional data of neuroplasticity-related genes showed that psychedelics influence the expression of higher numbers of genes in the PFC compared to the hippocampus (Jefsen et al., 2020; Nichols & Sanders-Bush, 2002). Similarly, stimulation of 5-HT2A receptors by the non-selective agonist DOI caused an increase in BDNF mRNA in the neocortex, whereas the opposite effect was observed in the hippocampus (Vaidya et al., 1997). Two isoforms exist of the BDNF protein in (i.e., mature BDNF and pro-BDNF) and these have opposite effects on neuroplasticity (Qiao et al., 2017). Depending on the psychedelic drug, the dose, and the duration of treatment, drug effects on mature vs proBDNF – and hence on neurogenesis – may differ. For example, an increase in proBDNF could explain the reduction in neurogenesis after an acute high dose of psilocybin in rats (Catlow et al., 2013). A similar rationale could explain why both acute and chronic treatment with LSD and DOI did not affect adult hippocampal neurogenesis (Jha et al., 2008). Taken together, these observations indicate that future studies are needed to elucidate the time- and dose-dependent effects of psychedelics on the regulation of BDNF signaling and neurogenesis. For BDNF signalling, investigations should happen at all levels of analysis, including transcription, protein synthesis (e.g. mature BDNF/proBDNF ratios), and receptor regulation (e.g. TrkB/p75Ntrp ratio), and should be site-specific (e.g. hippocampus, PFC, amygdala). With regard to neurogenesis, future studies should look into the effects of psychedelics on the various steps of the neurogenic process, such as differentiation, maturation, and early and late integration of the newborn neurons (Denob-Pippener & Jessberger, 2021). As a result, a better understanding of the pharmacokinetic-pharmacodynamic (PK/PD) relationships will be useful to inform dose selection in later trials. For example, if the PK/PD relationship between plasma drug exposure and BDNF would predict antidepressant activity, the former could be used as a biomarker for therapeutic efficacy and to select doses for clinical testing.

Second, and related to the previous point, there is a need to better understand the role of serotonin and other monoamine receptors in the psychobiological effects of psychedelics. Although activation of the 5-HT2A receptor is commonly accepted to underly the subjective effects of psychedelics, the involvement of other receptors in the long-term effects on neuroplasticity cannot be ruled. For example, psilocybin shows significant affinity for the 5-HT1A receptor (Tylls, Palenčík, & Horáček, 2014) and this receptor has been implicated in processes of neurogenesis and pattern separation (Schreiber & Newman-Tancredi, 2014). In fact, activation of post-synaptic 5-HT1A heteroreceptors by the biased agonist F15599 acutely improved spatial pattern separation in rats (van Goethem, Schreiber, Newman-Tancredi, Varney, & Prick-aerts, 2015). In line with our proposed model, the agonistic activity of psilocybin at this receptor might explain why pre-treatment with the 5-HT2A antagonist ketanserin did not affect the anhedonic effects of the drug observed in mice (Hesselgrave, Troppoli, Wulff, Cole, & Thompson, 2021). Furthermore, there is preliminary evidence to support a role for the sigma 1 receptor in the effects of psychedelics on neurogenesis. In fact, the effects of DMT on neurogenesis were completely blocked by co-administration of the sigma 1 antagonist BD1063 (Morales García et al., 2020). Based on these observations, it can be argued that the pharmacological differences between psychedelics might translate into differences in the way these drugs affect neuroplasticity and, in turn, pattern separation. Further studies are needed to better understand the degree of specificity of the 5-HT2A receptor for these effects. In this regard, research might benefit from using 5-HT2A ligands, such as 25CN-NBOH, having higher selectivity than the commonly used agonist DOI, which possesses significant affinity for other 5-HT receptor subtypes, notably the 5-HT2C receptor (Canal & Morgan, 2012; Jensen et al., 2020). If it is found that the 5-HT2A receptor is essential for mediating these effects, structure-based drug discovery might allow for the development of novel ligands possessing a PK/PD profile that better suits the proposed model of antidepressant activity.

Third, the role of the acute hallucinogenic experience in the long-term activation of the neuroplastic pathways proposed in this model is not understood. According to our hypothesis, the acute hallucinogenic
experience allows for the creation of awareness and disruption of negative cognitive schemas in depressed patients, allowing for a subsequent release of the cognitive grip induced by the latter and therefore an increase in cognitive flexibility and reduction in the negative bias. In this regard, the quality of the hallucinogenic experience was found to be an important predictor of the therapeutic outcome of psychedelic-assisted psychotherapy for MDD (Roseman, Natt, & Carhart-Harris, 2018). The quality of this experience is known to be strongly dependent on stimuli generating internally and externally, which are commonly known as “set” and “setting” (Harogsol, 2016). To validate our proposed model, it is important to investigate the relationship between the “set” and “setting” and their influence on the long-term effects of psychedelics on neuroplasticity. In rats, chronic pretreatment with corticosterone reversed the antidepressant effects of psilocybin on measures of anhedonia and anxiety (Jones et al., 2020; preprint). This suggest that chronic exposure to high levels of stress in the period preceding the hallucinogenic experience might lead to exacerbation of depressive symptoms. Yet, more studies are needed to draw valid conclusions.

Although we argue for a role of the acute subjective experience in the long-term antidepressant effects of psychedelics, the opposite can be argued as well. This idea is supported by evidence showing biological and behavioural alterations after subchronic administration of sub-hallucinogenic doses of LSD, a practice referred to as “microdosing” (Hutten et al., 2020a, 2020b; Kuypers, 2020). In fact, a review of trials involving microdosing in both healthy volunteers and patients has shown positive effects on measures of cognitive flexibility (Kuypers, 2020). Moreover, low doses of LSD (5–20 mcg) acutely increased mature BDNF levels in healthy humans and, contrary to the effects of hallucinogenic doses, it improved measures of sustained attention (Hutten et al., 2020a, 2020b). Promising results have been obtained also from a preclinical study in which intermittent administration of low non-hallucinogenic doses of DMT increased fear extinction in rats (Cameron et al., 2018; Cameron, Benson, DelFiech, Fiehn, & Olson, 2019). Although the effects of single hallucinogenic doses of psychedelics on neuroplasticity seem to persist even for several days after excretion (Ly et al., 2020), it can be argued that microdosing might provide a more steady stimulation of the biological mechanisms underlyng this process, and therefore potentially increase the therapeutic effects of the treatment. Moreover, this approach would increase the applicability of psychedelics in the general population. In fact, hallucinations can lead to temporary states of severe distress and anxiety in some patients undergoing treatment (Dos Santos et al., 2018) and clinical trials have therefore administered these drugs in supportive settings. This characteristic could lead to increased health care costs and decreased patient’s willingness to undergo treatment. On the other hand, the use of non-hallucinogenic doses would allow the patient to self-administer the drug on a regular basis, if needed, without strict supervision, and while maintaining their daily functioning. This could potentially also be achieved by developing non-hallucinogenic compounds, such as biased 5-HT2A agonists, that induce neuroplasticity without causing hallucinations. Based on the lack of head twitch responses observed in mice after administration, the latter being a validated measure for the hallucinogenic property of drugs, Olson and colleagues claimed to have developed such compounds (Cameron et al., 2021; Olson, 2020). Yet, further studies are needed to prove their antidepressant efficacy in both rodents and humans.

Fourth, there are differences in the PK/PD profile of the SRI vortioxetine and psychedelics and our model might benefit from evidence of increased pattern separation by drugs possessing a similar PK/PD profile. In this regard, ketamine might be of interest. There is initial evidence to suggest an antidepressant action of the NMDA receptor antagonist ketamine in MDD similar to the action of psychedelics. High similarities in the PK/PD relationship of the antidepressant effects of psychedelics and ketamine are present. In fact, a single intravenous infusion of hallucinogenic doses of the drug is able to induce antidepressant effects that can last for several weeks (Corriger & Pickering, 2019). Like psychedelics, there is strong evidence showing that the underlying mechanism of these effects involves the stimulation of cortical neuroplasticity and hippocampal neurogenesis (Ly et al., 2018, 2020; Murrough et al., 2013). Moreover, a study performed in mice provides initial evidence of long-term beneficial effects of ketamine on pattern separation (Mastrodakos et al., 2018). Taken together, these observations suggest that an improvement in pattern separation might be an indicator of antidepressant potential for different classes of drugs.

A final consideration regards the current COVID-19 pandemic and whether our proposed psychobiological model might apply for the mood alterations and cognitive dysfunctions which have been observed in COVID-19 survivors. Compared to healthy individuals, these patients show higher symptoms of depression and impairments in measures of sustained and selective attention, both of which are associated with activation of the immune-inflammatory system (Mazza et al., 2020; Zhou et al., 2020). Based on the observation that viruses, and especially coronaviruses, can lead to neuronal loss in the hippocampus (Ritchie, Chan, & Watermeyer, 2020), the neurogenesis-promoting effects of psychedelic compounds might be able to reverse these changes. Yet, future studies are needed to understand whether COVID-related cognitive dysfunctions include deficits in pattern separation.

In conclusion, we propose a translational framework for future investigations of the biological mechanisms underlying the therapeutic effects of psychedelics on depression. This framework might serve as a foundation for new mechanism-based drug development strategies that aim for the treatment of mental disorders that are characterized by abnormal cognitive functioning and impaired neuroplasticity. Although this model is somewhat speculative due to the lack of sufficient evidence, we believe that such strategies will lead to advances in a field which is currently struggling to provide new solutions for long-existing problems.

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