Changes in default-mode network activity and functional connectivity as an indicator of psychedelic-assisted psychotherapy effectiveness

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A b s t r a c t

The history of psychedelic drug use in psychotherapy spans over half of a century. Presently, psychedelic drugs are being studied as psychotherapy adjuncts. There are promising findings (Evans *et al*. 2018; Watts *et al*. 2017; Gasser *et al*. 2014) on the usage of such drugs as lysergic acid diethylamide, psilocybin, ketamine, and ayahuasca in the treatment of mood disorders. This may be an alternative way to solve the problem of treatment-resistant mood disorders.

Novel findings suggest that psychedelic drugs are capable of changing the neural mechanisms underlying mental dysfunction and producing long-lasting improvements in functioning of clinical populations. The alterations produced by these drugs are clustered in a set of regions – the default-mode network (DMN) – which are engaged in various intrinsic processes, e.g. forming internal experience and building self-narrative. Research shows that changes in the DMN are characteristic for mood disorders (Mulders *et al*. 2015; Kaiser *et al*. 2015), and for this reason the DMN can become a trigger for response to therapy. Alterations in the DMN may be a marker of psychedelic-assisted psychotherapy efficacy, as the state produced by psychedelics is characterised by a pattern of DMN functioning in an opposite way to that seen in mood disorders.

In this narrative review we will take a closer look at how some psychedelics effect DMN activity and functional connectivity, sum up the proposed interpretations of such changes, compare those results to findings in the field of mood disorders (mainly depression), and propose future directions for research on psychedelic-assisted psychotherapy.

Key words: default-mode network, depression, mood disorders, psychedelic, therapy.

Introduction

Psychedelic drugs are a group of psychoactive compounds that produce an altered state of consciousness, e.g. altered perception, tactile enhancement, emotion enhancement, self-disintegration, and sense of connection to the world and other people. Lysergic acid diethylamide (LSD), psilocybin, mescaline, and N,N-dimethyltryptamine (DMT) are examples of substances typically included in this group. Drugs such as ketamine, 3,4-methylenedioxymethamphetamine (MDMA), and cannabis are also related to this group because they share some properties of psychedelic drugs.

For the last decade, neuroscientists and psychologists have actively explored the properties of this group of psychoactive substances. They have tried to establish the risks and benefits coming from psychoactive substance use because it is important due to both the controversies surrounding psychoactive substance use and their positive properties. Not only have researchers revealed the impact of psychedelics on the brain and behaviour (Carhart-Harris *et al.* 2012, 2016; Müller *et al.* 2018; Scheidegger *et al.* 2012; Palhano-Fontes *et al.* 2015), but they have also proposed the implications of psychedelic use in the psychotherapy of depression, anxiety, post-traumatic stress disorder (PTSD), and addiction (Carhart-Harris *et al.* 2017; Evans *et al.* 2018; Watts *et al.* 2017; Gasser *et al.* 2014; Oehen *et al.* 2013; Thomas *et al.* 2013).

As Carhart-Harris *et al.* (2017) and Evans' team (2018) have shown, changes after psychedelic-assisted psychotherapy are also seen

on the neural level. They observed changes in the default-mode network (DMN), a set of brain regions whose activation is positively correlated and associated with rest. The major hubs of the DMN are the posterior cingulate cortex (PCC), and precuneus and medial prefrontal cortex (mPFC). They are involved in the processing of internal experience: building self-narrative, mind-wandering, planning the future, and evaluating events from the past (Whitfield-Gabrieli and Ford 2012). Dysfunction of the DMN (abnormal activity of main DMN hubs and altered functional connectivity [FC] within DMN/between DMN and other networks) was found in individuals with major depression disorder (MDD), bipolar disorder, schizophrenia, and other psychiatric disorders (Whitfield-Gabrieli and Ford 2012). Increased activity of main DMN nodes, disintegration within the DMN, and abnormal FC with various other structures (e.g. the insula, hippocampus, dorsal-medial prefrontal cortex) was found in individuals with MDD (Mulders *et al.* 2015; Kaiser *et al.* 2015). These findings were associated with increased rumination, deterioration of cognitive functioning, and impaired processing of emotional stimuli. In contrast, psychedelic drugs seem to provide the opposite pattern: they level DMN activity and reduce positive coupling between its main nodes (Carhart-Harris *et al.* 2012, 2016; Scheidegger *et al.* 2012).

Based on previous research of mood disorders and psychedelic substances, it is suggested that the DMN may be one of the possible candidates reflecting the psychotherapeutic effect of psychedelic drugs. However, each study of a particular substance reports a slightly different model of DMN functioning, although researchers tend to interpret observed changes in terms of MDD-related symptom reduction.

We collected information on changes in the DMN produced by psychedelics and DMN functioning in individuals with mood disorders. We searched PubMed and Google Scholar for articles published in the period from 2010 till 2018 using the keywords: psilocybin, LSD, ayahuasca, DMT, ketamine, DMN, depression, mood disorders, psychedelics, psychotherapy, and fMRI (functional magnetic resonance imaging).

Neural underlays of psychoactive substance effects

Psilocybin

Psilocybin is a psychoactive compound that is naturally occurring in psilocybin mushrooms.

Psilocybin mushrooms have a long history of human use. For instance, they were used in ancient ceremonies and rituals by the Aztecs and Maya (Carod-Artal 2015). Psilocybin produces profound psychedelic effects; the results of a single intake are long-lasting and are characterised by acceptance towards one's emotions, and a feeling of connectedness to one's self and others (Watts *et al.* 2017).

Once in the body psilocybin transforms to psilocin, and psilocin acts as a partial agonist for several serotonin receptors (5-HT2B, 5-HT2C, 5-HT2A). Psilocin activation of 5-HT2A receptors plays a major role in producing an altered state of consciousness. This receptor is distributed throughout the neocortex and is involved in functions such as mood, learning, and anxiety. Some controversies remain on how exactly psilocin (and other psychedelic drugs) act via the the 5-HT2A receptor: some propose that activation of 5-HT2A may mediate activity of layer V glutamatergic neurons (thus, casing excitation), while other observations suggest that 5-HT2A receptors are also found on GABAergic interneurons exerting an inhibitory effect (Lee and Roth 2012).

In studies using fMRI, Carhart-Harris *et al.* (2012) found decreases in blood-oxygen level-dependent (BOLD) signal and cerebral blood flow (CBF) after psilocybin intake. Deactivations were found in the anterior cingulate cortex (ACC)/mPFC, and thalamic and posterior regions. However, only decreased CBF in the ACC/mPFC was significantly correlated with the subjective intensity of effects. Another finding of this research was decreased FC within the DMN: positive coupling between the mPFC and PCC was significantly reduced during a "psilocybin" scan. When put in the context of changes observed in some studies on depression, where resting state functional connectivity (RSFC) between the mPFC and PCC increased, the findings of Carhart-Harris *et al.* (2012) seems somewhat appealing because they give space to speculate about the therapeutic properties of psilocybin. However, a recent study of the same research group (Carhart-Harris *et al.* 2017) focusing on the effects of psilocybin on depressed patients, found increased FC within the DMN the day after drug intake (for summary see Table 1). Intriguingly, this finding (along with the ventromedial prefrontal cortex-bilateral inferior lateral parietal cortex [vmPFC-ilPC]) of FC was predictive of treatment response at five weeks. Interpreting this and previous findings, the authors emphasise inconsistency in the findings on FC within the DMN in individuals with MDD

because some studies show increased FC while others show decreased (Mulders *et al.* 2015).

Lysergic acid diethylamide

LSD is a classic psychedelic, first synthesised in 1938 by Albert Hofmann and tried in 1943 by its inventor. Like psilocybin, the psychoactive effects of LSD are determined by its serotonin receptor (5-HT2A) agonism (Vollenweider and Kometer 2011). The effects of LSD somewhat resemble those of psilocybin but have a longer duration (8–12 hours). The psychotherapeutic effects of LSD have been studied since the 1950s by psychotherapists (Grof 1972; Baker 1964), but only recently has research on LSD made its way from underground. In 2014, the first clinical trial on LSD use in the psychotherapy of anxiety associated with life-threatening diseases was completed by Swiss psychotherapist Peter Gasser (2014) and his research group. Follow-up measurement two months after treatment showed a significant reduction in the anxiety symptoms measured by State-Trait Anxiety Inventory (STAI), and this reduction was sustained for 12 months.

Consistent with findings on psilocybin, a few studies (Carhart-Harris *et al.* 2016; Müller *et al.* 2018) found decreased FC within the DMN. Carhart-Harris *et al.* (2016) also found decreased positive coupling between parahippocampal (PH) regions and the PCC and retrosplenial cortex (see Table 1). This result correlated with subjective rankings of self-dissolution. However, in Müller *et al.*'s (2018) study decreased within-DMN FC did not correlate with intensity of self-dissolution.

Ayahuasca

Ayahuasca is a brew consisting of a DMT-containing plant (such as *Mimosa hostilis*) and a mono-amine oxidase inhibitor-containing plant (such as *Banisteriopsis caapi*). DMT acts as a 5-HT2A agonist, and the MAOI prolongs DMT action. According to user reports, ayahuasca produces strong visual alterations, hallucinations, and a profound mystical experience. Ayahuasca has been used by peoples of the Amazon in healing and religious rituals and is now gaining wider popularity among people from around the world. Preliminary evidence for ayahuasca-assisted treatment of substance dependence were obtained by Fernández *et al.* (2013), Loizaga-Velder *et al.* (2014), and Thomas *et al.* (2013). They found that ayahuasca intake was associated with a reduction in dependence symptoms.

Palhano-Fontes *et al.* (2015) found that ayahuasca (similarly to psilocybin) lowers DMN activity. Additionally, they found decreased FC within the PCC/precuneus (the authors explain this finding as a possible marker of an altered state of consciousness) but did not find significant changes in mPFC-PCC coupling (see Table 1). Bouso *et al.* (2015) explored changes connected with long-term ayahuasca use. They found decreased cortical thickness (CT) in the PCC and increased CT in the ACC (structure involved in attentional processing) in regular ayahuasca users. Decreased CT in the PCC correlated with duration and intensity of substance use and with scores on personality traits measuring religiousness, transpersonal feelings, and spirituality.

Ketamine

Ketamine is a substance used in medicine for starting and maintaining anaesthesia. Ketamine is also used as a recreational drug because it produces a range of specific mind-altering effects, including "out-of-body" experiences, trans-like states, self-disintegration, and euphoria. Unlike

Table 1. Summary of main psychedelic-induced changes in default-mode network connectivity and activity

Study	Substance	Within-DMN connectivity	DMN FC with other regions
Carhart-Harris *et al.* 2016	LSD	decreased*	DMN-parahippocampal regions – decreased
Müller *et al.* 2018	LSD	decreased*	widely increased between-network connectivity
Carhart-Harris *et al.* 2012	psilocybin	decreased*	increased DMN-TPN connectivity
Carhart-Harris *et al.* 2017	psilocybin	increased**	increased connectivity vmPFC-ilPC
Palhano-Fontes *et al.* 2015	ayahuasca	decreased*	NA
Bonhomme *et al.* 2016	ketamine	decreased*	NA
Scheidegger *et al.* 2013	ketamine	decreased**	NA
Evans *et al.* 2018	ketamine	increased***	increased DMN-SN (in particular insula), CEN in MDD subjects

Within-DMN connectivity – correlation in activity of default-mode network (DMN) regions, DMN FC with other regions – correlation in activity of DMN regions with other regions/networks, TPN – task-positive network, vmPFC-ilPC – ventromedial prefrontal cortex-bilateral inferior lateral parietal cortex, SN – salience network, CEN – central-executive network, MDD – major depression disorder, NA – no information available, *under a drug, **day after a drug, ***two days after a drug

other compounds included in the present review, ketamine acts as a NMDA receptor (receptor of main excitatory neurotransmitter – glutamate) antagonist (Bergman 1999). NMDA receptors are involved in various brain functions, including memory and learning (synaptic plasticity).

A meta-analysis (McGirr *et al.* 2015) of seven randomised, double-blind, placebo-controlled studies on ketamine use in the psychotherapy of MDD yielded the effectivity of single ketamine infusions in reducing depression symptoms (follow-ups were after three, seven, and 14 days). The exact neuronal mechanism of ketamine-assisted treatment remains ambiguous; it is hard to establish whether it is NMDA antagonism that is responsible for the therapeutic effects of the compound, because some studies suggest that NMDA agonists also have antidepressant properties (Huang *et al.* 2013).

Research on functional changes induced by ketamine give some promising results. Reduced FC between the PCC and dmPFC, mPFC, and perigenual ACC two days after ketamine administration in healthy volunteers was found by Scheidegger *et al.* (2012). The authors focused on the dorsal-medial PFC (dmPFC) because it was proposed in earlier literature that this region has hyperconnectivity with different networks, including the DMN in MDD (see Table 1). The results were interpreted in terms of the antidepressant effects of ketamine. Another study (Bonhomme *et al.* 2016) also found decreased FC within the DMN during light ketamine-induced sedation; this effect was more profound during ketamine-induced unresponsiveness (see Table 1).

A recent study by Evans *et al.* (2018) investigated changes two and 10 days after a single dose of ketamine in individuals with MDD and in healthy controls (HC). They found different changes in healthy and MDD individuals after a session with ketamine: increased FC of the DMN and insula, increased FC of the posterior DMN (PCC), and regions overlapping with central executive (CEN) and salience networks (SN) were observed in individuals with MDD, while increased global connectivity was found in healthy subjects. Alterations in the FC of the insula and the DMN may reflect some symptomatic mechanisms that are relevant for depression: processing and interpretation of emotional stimuli and switching between the CEN and the DMN (see Table 1). Hence, normalisation of FC between the insula and the DMN may reflect improvement in symptoms. A second finding consistent with the hypothesis that FC

between the CEN, SN, and DMN is disturbed in MDD (Evans *et al.* 2018; Mulders *et al.* 2015), proposing an increase in FC in overlapping regions may also be marker of a positive shift after ketamine intake. Changes observed in the HC are counterintuitive when taking into account the decreases within DMN FC found by previous research the day after a ketamine session. This may be due to slightly different timing in measurements. Increases in the global connectivity observed after ketamine in HC are also somewhat consistent with the findings of Carhart-Harris *et al.* (2017), who reported increases in RSFC within the DMN after treatment with psilocybin.

Below (Table 1) we summarise the information on how different psychoactive substances change FC within DMN regions and the FC of DMN hubs to other brain areas.

Changes associated with psychological dysfunction and their alteration after psychedelic drug administration

DMN activity is associated with internal thoughts and anticorrelated with task performance (e.g. the harder the task, the stronger the suppression of DMN activity [Whitfield-Gabrieli and Ford 2012]). The inability to suppress activity of the DMN was found in patients with MDD, suggesting that the processing of internal thought interferes with the ability to concentrate on a task (Whitfield-Gabrieli and Ford 2012). This may be one path of reasoning to explain the cognitive deficits accompanying MDD. Additionally, Hamilton *et al.* (2011) found greater DMN activity than task-positive network activity in individuals with MDD. Overall, those findings suggest that an impaired ability to suppress ruminative processes in patients with MDD is associated with greater DMN activation. Putting this in the frame of studies on psilocybin and ayahuasca, the inhibiting effect on the DMN found by Carhart-Harris *et al.* (2014) and Palhano-Fontes *et al.* (2015) suggest that those substances may reduce maladaptive self-reference symptoms. Other studies mentioned in this review concentrated mainly on FC of the DMN, rather than evoked activity.

Increased positive correlation in evoked activity (functional connectivity) of the DMN nodes was repeatedly found in individuals with MDD (for meta-analysis and review see: Mulders *et al.* 2015; Kaiser *et al.* 2015; Whitfield-Gabrieli and Ford 2012). These results can be

interpreted in terms of increased intrinsic attention and rumination. On the other hand, as we mentioned earlier, there are studies showing decreased FC within the DMN in individuals with MDD (Guo *et al.* 2014; Zhu *et al.* 2012; Chen *et al.* 2015; Mulders *et al.* 2016) or no alterations in FC (Sexton *et al.* 2012; Veer *et al.* 2010). This heterogeneity of findings could appear as a result of different methods of analysis (e.g. independent component analysis versus seed-based analysis) and different study designs (differences in age of participants and intensity of MDD symptoms). For instance, as Mulders *et al.* (2015) report in their meta-analysis, some groups using independent component analysis found decreased FC or no changes in FC, whilst seed-based correlation analysis studies reported mainly increased FC within the DMN. The other possible explanation for the inconsistency may be different patterns of network FC associated with different depression subtypes, as shown by Drysdale *et al.* (2017). Subtype differences are usually not taken into account in studies on the DMN alteration in depression, so it is an interesting field for exploration. There is a possibility that exploration of the DMN FC with other regions may help to better understand the observed differences.

The increases in within-DMN FC observed by Carhart-Harris *et al.* (2017) after psilocybin treatment and the increases in global connectivity observed by Evans *et al.* (2018) two days after ketamine intake (in healthy subjects) are counterintuitive when compared to earlier findings showing decreases within DMN FC during psilocybin-induced altered states of consciousness (Carhart-Harris *et al.* 2014), the day after ketamine administration (Scheidegger *et al.* 2012), and during ketamine intoxication (Bonhomme *et al.* 2016). Evans *et al.* (2018) propose that the observed finding may "reflect a re-normalisation effect" occurring after drug intake. The same may be applied to Carhart-Harris *et al.*'s (2017) findings; it is possible that increases a few days after drug intake are the result of a rebound effect resulting in formatting of new patterns of information processing. Nichols (2016) suggests that the psychotherapeutic effects of psychedelics are linked to temporal alteration that they provide in connectivity patterns of the DMN.

"Increased intrinsic attention" correlated with increased within DMN FC does not necessarily underlie pathological processes. For instance, meditation, like psychedelics, evokes a rumination-restraint process and produces a pattern of functioning opposite to that observed in indi-

viduals with MDD (Simon and Engström 2015). It can be an example of a case in which increased within-DMN FC reflects positive changes. Jang *et al.* (2011) showed that practitioners of brain-wave vibration meditation (a kind of moving meditation consisting of performing natural rhythmic movements and focusing on bodily sensations) have increased within-DMN FC. The finding of another group (Taylor *et al.* 2012) showed that experienced mindfulness meditators had increased within-DMN FC. Nevertheless, there are not enough findings to properly support this hypothesis.

Taken together, increased FC observed after psychedelic drug administration may not reflect ruminative mechanisms (as in the case of depression), but rather altered self-referential processing following the disintegration of the self, which is persistent during drug intoxication, and which, in turn, correlates with decreased within-DMN coupling. Nevertheless, this suggestion remains speculative and needs further investigation.

Another aspect of changes of DMN FC relates to DMN FC with other regions. Evans *et al.* (2018) found that DMN FC with the insula reflected the progress of treatment. They also found changes in FC with the CEN, which is impaired in individuals with MDD (Mulders *et al.* 2015). FC between the DMN and hippocampus is increased in MDD (Kaiser *et al.* 2015). Decreased FC between the parahippocampal region and DMN was found after use of LSD (Carhart-Harris *et al.* 2016) and psilocybin (Lebedev *et al.* 2015). In those studies, decoupling was associated either with self-dissolution (Carhart-Harris) or with the psychotic-like effects of the compound (Lebedev *et al.* 2015).

The field of DMN FC with other regions or networks during altered states of consciousness is still unstudied, as Müller *et al.* (2018) suggested. However, there is preliminary evidence implying that between-network FC is also involved in the effects of the drugs and may also take part in treatment outcomes. Although research on DMN activity and FC is the focus of the present paper, it is only one of the possible approaches to study the efficacy of psychedelics in the treatment of MDD. Some other processes are worth mentioning, to build a broad, multifaceted concept of the psychotherapeutic potential of psychedelic drugs. Intriguing and important findings also lie in the field of neurobiology: Vollenweider and Kometer (2011) collected information on glutamate-driven neuroplasticity caused by psychedelics and its role in treating

mood disorders. They proposed that psychedelic drugs (ketamine, LSD, and psilocybin) may retrieve healthier patterns of neural functioning via regulation of neuronal plasticity in prefrontal-limbic circuitries. Perhaps, functional changes observed in fMRI studies and long-lasting behavioural changes are also the result of neuroplasticity processes.

Conclusions

Summing up, there is preliminary evidence that psychedelics produce long-lasting positive changes in behaviour and may be an effective adjunct in the therapy of mood disorders (Carhart-Harris *et al.* 2017; Evans *et al.* 2018; Gasser *et al.* 2014; McGirr *et al.* 2015; Loizaga-Velder *et al.* 2014; Oehen *et al.* 2013; Watts *et al.* 2017). The possible neural underlay of these changes may be an altered functioning of structures engaged in building self-narration and emotion processing. It is suggested that MDD may be associated with maladaptive increases in intrinsic attention, while psychedelic drugs seem to effectively transform processes implicated in the pathology of MDD via modulation of DMN activity and FC. So far, inconsistencies in research on psychedelic outcomes are already beginning to appear, and we are not able to obtain a complete picture of DMN alterations. Moreover, Müller *et al.* 2018 noted that changes in DMN FC observed under LSD closely resemble changes produced by the non-psychoactive selective serotonin reuptake inhibitor sertraline. This suggests that we may only be at the beginning of the journey towards understanding psychedelic-induced changes. Because the field of studies on psychedelics use in psychotherapy is new, a major challenge for now is the low number of replications, low number of studies on clinical populations, low number of participants, and the absence of a widely accepted data collection and analysis approach.

Psychedelic drugs have a controversial history of use; for this reason, it is crucial to objectively estimate the possible risks and benefits of psychoactive substance use. To our knowledge, there have been no adverse events observed in the therapeutic setting with psilocybin (Gasser *et al.* 2014; Watts *et al.* 2017), and the population using psychedelic drugs are no more likely to be exposed to mental health problems (Johansen and Krebs 2015; Hendricks *et al.* 2015). Moreover, Hendricks *et al.* in 2015 found that psychedelic drug use is associated with reduced psychological distress and suicidality. A recent paper (Mason and Kuypers 2018) based on an online-questionnaire reported the efficacy of self-medication practices with psychedelics among responders. Still, psychedelic drugs are capable of producing psychosis-like episodes and adverse effects in some cases (Lebedev *et al.* 2015; Vollenweider *et al.* 1998), and it should be taken into account by therapists deciding to use psychedelic drugs in their practice.

The last important issue we would like to stress is the challenge of integrating psychedelic experiences and the following consolidation of therapy outcomes. From research (Watts *et al.* 2017; Gasser *et al.* 2014) we know that improvements after psilocybin/LSD-assisted psychotherapy can last for up to several month, although it would be interesting to explore whether those changes are visible on the neural level. The case with ketamine and ayahuasca is different because the alterations cannot be perceived as an outcome of psychedelic-assisted psychotherapy, but rather as an outcome of substance use and experience itself. This is because research on these substances focuses on substance-induced changes outside the context of additional psychotherapy. It would be interesting to compare whether psychotherapy enhances the positive outcomes of those substances and helps to consolidate experience, and whether those differences are observable on the neural level.

References

1. Baker EF. The use of lysergic acid diethylamide (LSD) in psychotherapy. Can Med Assoc J 1964; 91: 1200.
2. Bergman SA. Ketamine: review of its pharmacology and its use in pediatric anesthesia. Anesthesia progress 1999; 46: 10.
3. Bonhomme V, Vanhaudenhuyse A, Demertzi A, et al. Resting-state network-specific breakdown of functional connectivity during ketamine alteration of consciousness in volunteers. Anesthesiology 2016; 125: 873-888.
4. Bouso JC, Palhano-Fontes F, Rodríguez-Fornells A. Long--term use of psychedelic drugs is associated with differences in brain structure and personality in humans. Eur Neuropsychopharmacol 2015; 25: 483-492.
5. Carhart-Harris RL, Erritzoe D, Williams T, et al. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A 2012; 109: 2138-2143.
6. Carhart-Harris RL, Muthukumaraswamy S, Roseman L, et al. Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proc Natl Acad Sci U S A 2016; 113: 4853-4858.
7. Carhart-Harris RL, Roseman L, Bolstridge M, et al. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci Rep 2017; 7: 13187.
8. Chen Y, Wang C, Zhu X, et al. Aberrant connectivity within the default mode network in first-episode, treatment-naive major depressive disorder. J Affect Disord 2015; 183: 49-56.

9. Carod-Artal FJ. Hallucinogenic drugs in pre-Columbian Mesoamerican cultures. Neurología 2015; 30: 42-49.

10. Drysdale AT, Grosenick L, Downar J, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 2017; 23: 28-38.

11. Evans JW, Szczepanik J, Brutsché N, et al. Default mode connectivity in major depressive disorder measured up to 10 days after ketamine administration. Biol Psychiatry 2018; 84: 582-590.

12. Fernández X, dos Santos RG, Cutchet M, et al. Assessment of the psychotherapeutic effects of ritual ayahuasca use on drug dependency: A pilot study. In: The therapeutic use of ayahuasca, Labate BC, Cavnar C (eds.). Springer, Berlin, Heidelberg 2015: 183-196.

13. Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis 2014; 202: 513.

14. Grof S. Varieties of transpersonal experiences: Observations from LSD psychotherapy. J Transpersonal Psy 1972; 4: 45.

15. Guo W, Liu F, Zhang J, et al. Abnormal default-mode network homogeneity in first-episode, drug-naive major depressive disorder. PLoS ONE 2014; 9: e91102.

16. Hamilton JP, Furman DJ, Chang C, et al. Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. Biol Psychiatry 2011; 70: 327-333.

17. Hendricks PS, Thorne CB, Clark CB, et al. Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. J Psychopharmacol 2015; 29: 280-288.

18. Huang CC, Wei IH, Huang CL, et al. Inhibition of glycine transporter-I as a novel mechanism for the treatment of depression. Biol Psychiatry 2013; 74: 734-741.

19. Jang JH, Jung WH, Kang DH, et al. Increased default mode network connectivity associated with meditation. Neurosc Lett 2011; 487: 358-362.

20. Johansen PØ, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: A population study. J Psychopharmacol 2015; 29: 270-279.

21. Kaiser RH, Andrews-Hanna JR, Wager TD, et al. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA psychiatry 2015; 72: 603-611.

22. Lebedev AV, Lövdén M, Rosenthal G, et al. Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. Hum Brain Mapp 2015; 36: 3137-3153.

23. Lee HM, Roth BL. Hallucinogen actions on human brain revealed. Proc Natl Acad Sci U S A 2012; 109: 1820-1821.

24. Loizaga-Velder A, Verres R. Therapeutic effects of ritual ayahuasca use in the treatment of substance dependence–qualitative results. J Psychoactive Drugs 2014; 46: 63-72.

25. Mason NL, Kuypers KP. Mental health of a self-selected sample of psychedelic users and self-medication practices with psychedelics. J Psychedelic Stud 2018: 1-8.

26. McGirr A, Berlim MT, Bond DJ, et al. A systematic review and meta-analysis of randomized, double-blind, place-bo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med 2015, 45: 693-704.

27. Mulders PC, van Eijndhoven PF, Schene AH, et al. Resting-state functional connectivity in major depressive disorder: a review. Neurosci Biobehav Rev 2015; 56: 330-344.

28. Mulders PC, van Eijndhoven PF, Pluijmen J, et al. Default mode network coherence in treatment-resistant major depressive disorder during electroconvulsive therapy. J Affect Disord 2016; 205: 130-137.

29. Müller F, Dolder PC, Schmidt A, et al. Altered network hub connectivity after acute LSD administration. Neuroimage: Clin 2018; 18: 694-701.

30. Nichols DE. Psychedelics. Pharmacol Rev 2016; 68: 264-355.

31. Oehen P, Traber R, Widmer V, et al. A randomized, controlled pilot study of MDMA (±3, 4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). J Psychopharmacol 2013; 27: 40-52.

32. Palhano-Fontes F, Andrade KC, Tofoli LF, et al. The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. PLoS ONE 2015; 10: e0118143.

33. Scheidegger M, Walter M, Lehmann M, et al. Ketamine decreases resting state functional network connectivity in healthy subjects: implications for antidepressant drug action. PLoS ONE 2012; 7: e44799.

34. Sexton CE, Allan CL, Le Masurier M, et al. Magnetic resonance imaging in late-life depression: multimodal examination of network disruption. Arch Gen Psychiatry 2012; 69: 680-689.

35. Simon R, Engström M. The default mode network as a biomarker for monitoring the therapeutic effects of meditation. Front Psychol 2015; 6: 776.

36. Taylor VA, Daneault V, Grant J, et al. Impact of meditation training on the default mode network during a restful state. Social cognitive and affective neuroscience 2012; 8: 4-14.

37. Thomas G, Lucas P, Capler NR, et al. Ayahuasca-assisted therapy for addiction: results from a preliminary observational study in Canada. Curr Drug Abuse Rev 2013, 6: 30-42.

38. Veer IM, Beckmann C, Van Tol MJ, et al. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. Front Syst Neurosci 2010; 4: 41.

39. Vollenweider FX, Kometer M. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Nat Rev Neurosci 2010; 11: 642.

40. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bäbler A, et al. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport 1998; 9: 3897-3902.

41. Watts R, Day C, Krzanowski J, et al. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. J Humanist Psychol 2017; 57: 520-564.

42. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol 2012; 8: 49-76.

43. Zhu X, Wang X, Xiao J, et al. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biol Psychiatry 2012; 71: 611-617.