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Don't be afraid, try to meditate- potential effects on neural activity and connectivity of psilocybin-assisted mindfulness-based intervention for social anxiety disorder: A systematic review

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ABSTRACT

Background: Current first-line treatment for social anxiety disorder (SAD), one of the most prevalent anxiety disorders, is limited in its efficacy. Hence, novel treatment approaches are urgently needed. The current review suggests a combination of meditation-based interventions and the administration of a psychedelic as a future alternative treatment approach. While both separate treatments show promise in the treatment of (other) clinical conditions, their combination has not yet been investigated in the treatment of psychopathologies.

Aim: With a systematic literature review, we aim to identify the potential mechanisms by which combined psilocybin and mindfulness treatment could adjust anomalous neural activity underlying SAD and exert therapeutic effects.

Results: Thirty experimental studies investigating the neural effects of meditation or psilocybin treatment in healthy and patient samples were included. Findings suggest that psilocybin-assisted meditation interventions might change cognitive processes like biased attention to threat linked to SAD by modulating connectivity of the salience network, balancing the activity and connectivity of cortical-midline structures, and increasing fronto-parietal control over amygdala reactivity.

Conclusions: Future studies should investigate whether psilocybin-assisted mindfulness-based intervention can provide therapeutic benefits to SAD patients who are do not remit following conventional therapy.

1. Introduction

Anxiety disorders have been identified as the most common mental disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Bandelow and Michaelis, 2015). Among these, social anxiety disorder (SAD) is one of the most frequently encountered conditions. Global prevalence estimates indicate a 12-month prevalence of 2.4% and a lifetime prevalence of approximately 4 % (Stein et al., 2017). Individuals affected by SAD suffer from acute fear or anxiety provoked by specific social situations (American Psychiatric Association, 2013), which impairs their social relationships, academic achievements, work productivity, and overall quality of life (Lipsitz and Schneier, 2000). Accordingly, SAD causes high personal distress and immense economic costs, mainly due to the lost or reduced productivity of the individual (DuPont et al., 1996). Additionally, SAD is characterized by an early onset, and it develops into a chronic condition if left untreated. Patients suffering from SAD have a higher risk of developing comorbid disorders, especially major depression and substance abuse (Stein and Stein, 2008).

To gain a better insight into the pathology of SAD, the underlying psychological and neurobiological mechanisms have been researched. Focusing on the neurobiology related to psychological symptoms has led to developing and improving novel evidence-based treatment options (Mathew et al., 2008). To provide a guideline for identifying potential treatment mechanisms for SAD, Fig. 1 proposes a model that, based on Hofmann (2007), links the psychological factors maintaining SAD to anomalous neural activity and network connectivity.

Constant preoccupation with the fear of being negatively evaluated by others represents one of the core symptoms experienced by SAD patients, followed by the development of unreasonably high self-directed social standards and poorly defined social goals which leads to social apprehension (Stein and Stein, 2008). Additionally, biased

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attention allocation towards socially threatening stimuli (e.g., angry faces) was shown in SAD and associated with increased activity of the anterior insula and aberrant functional connectivity (FC) of the salience network (SN) (Heinrichs and Hofmann, 2001); the latter being involved in attention allocation to the self, and switching between neurocognitive networks (Seeley et al., 2007). During a social encounter, SAD patients' attention to self-referential processes in increased, which has been linked to increased FC between the SN and default mode network (DMN), and excessive activation of the medially located DMN structures, including the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC)/precuneus (Pannekoek et al., 2013; Yoon et al., 2019). Additionally, the DMN was decoupled from other networks, such as the limbic and ventral attention networks (Bruehl et al., 2014). This heightened self-awareness leads to increased awareness of their internal fear response (Yoon et al., 2019), intensifies negative self-perception, and makes it impossible for patients to observe external information, such as social feedback, that could disconfirm their fears.

Negative self-perception has been linked to delayed activation of the dorsolateral prefrontal cortex (dlPFC) (Goldin, Manber-Ball et al., 2009). The FC between the dlPFC, which usually exerts cognitive control over limbic structures, and the PCC (Miller and Cohen, 2001), was found to be reduced in response to social threats in SAD. This reduction in connectivity was linked to hyperactivity of the amygdala and insula (Etkin and Wager, 2007; Liao et al., 2010) and, on a psychological level, to lowered (cognitive) emotion regulation eliciting emotional hyper-reactivity (Goldin et al., 2009). SAD patients ultimately identify their social skills as poor and overestimate social costs generating an overall negative perception of the situation, which impacts their performance (Hofmann, 2007). Accordingly, SAD patients anticipate social mishaps, and engage in avoidance and safety behaviors. Following the perception of a social mishap, the rumination has been linked to increased FC within DMN structures (mPFC and PCC) during resting-state, which suggests engagement in self-focused processing of autobiographical memories (Rabany et al., 2017). Negative evaluation of the social encounter during post-event rumination reinforces the experience of social apprehension creating a vicious cycle of symptom maintenance.

Based on the information about changes in brain activity and connectivity related to SAD symptoms, one treatment approach could be to address brain processes and try to normalize those. Conventional treatment of SAD with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and cognitive behavior therapy (CBT) has been linked to decreased activity in cortical midline structures such as the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and PCC during eye contact (Schneier et al., 2011), as well as lowered activation of the amygdala and insula during

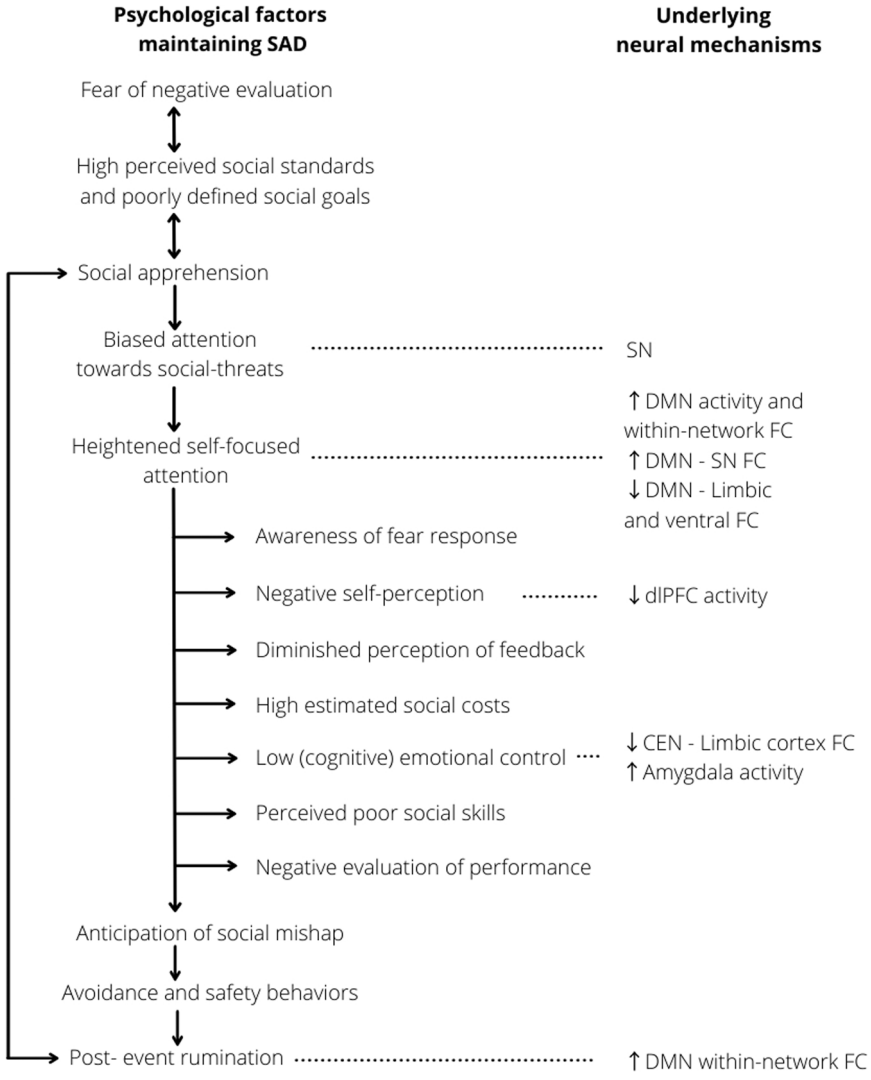

Fig. 1. Neuropsychological model of SAD based on the psychological model proposed by Hofmann (2007) and adjusted to include the neural correlates; *Abbreviations= SN= Salience Network; DMN= Default mode network; FC= functional connectivity; dlPFC= dorsolateral prefrontal cortex; CEN= central executive network.*

public speaking (Furmark et al., 2002), two types of social behavior that are commonly feared in SAD. Despite these effects, a substantial number of patients do not respond to this treatment. Several placebo-controlled pharmacological trials have investigated the efficacy of SSRIs and SNRIs for SAD, reporting response rates ranging from 43% to 71% (Nagata et al., 2015). The outcome of CBT treatment is comparable to pharmacological interventions with 50–60% of patients showing improvement in their condition (Eskildsen et al., 2010; Hofmann and Smits, 2008).

To date, five clinical trials have assessed potential benefits of the combination of a pharmacological SSRI treatment with and psychological therapy in SAD patients (Bernik et al., 2018; Blomhoff et al., 2001; Davidson et al., 2004; Gingnell et al., 2016; Nordahl et al., 2016). The treatment duration ranged between 9 and 26 weeks, during which participants received daily drug medication and weekly therapy sessions. In two trials, the combined treatment of the SSRI (sertraline (Bernik et al., 2018) and escitalopram (Gingnell et al., 2016)) and psychotherapy (group psychodynamic therapy and group CBT (Bernik et al., 2018) and internet-delivered CBT (Gingnell et al., 2016)) showed superior effects treatment effects compared to pharmaco- or psychotherapy alone. Unlike these trials, the study by Blomhoff et al. (2001) showed that the combined treatment SSRI (sertraline)-psychotherapy (exposure therapy) and the SSRI alone were both superior compared to placebo. Furthermore, psychotherapy (comprehensive CB group therapy or cognitive therapy) combined with pharmacotherapy (SSRI: fluoxetine or paroxetine) showed either no difference in efficacy from treatments alone or was less effective than cognitive therapy alone (Davidson et al., 2004; Nordahl et al., 2016). While further research on the efficacy of conventional treatment and the combined use of pharmacological and psychotherapy is needed, the results suggest that around one-half to one-third of the patients do not show significant improvements, emphasizing the need for novel treatment approaches. As activity changes in structures related to self-referential processing and cortico-limbic connectivity have been associated with symptom improvements (Freitas-Ferrari et al., 2010; Yoon et al., 2019), novel treatment approaches should target these neural processes.

Mindfulness meditation (MM) has been proposed as an alternative treatment for SAD (Koszycki et al., 2007). MM can be defined as training nonjudgmental awareness of one's thoughts and experiences. It teaches strategies to regulate one's emotions and become more open-minded about self-related thoughts (Kabat-Zinn, 2003). Mindfulness-based interventions focus on acquiring these relevant skills and aim to improve a patient's ability to cope with emotional and attentional reactions related to their pathology. To date, eight clinical trials testing the effects of MM in clinical samples with SAD have been conducted (Boettcher et al., 2014; Cassin and Rector, 2011; Goldin et al., 2013; Goldin and Gross, 2010; Jazaieri et al., 2012; Koszycki et al., 2007, 2016; Thurston et al., 2017). All indicate that mindfulness-based interventions, compared to active control groups (e.g., aerobic exercise), significantly reduce symptoms of SAD and improve patients' well-being and quality of life. Accordingly, MM and CBT seem to have comparable treatment outcomes (Thurston et al., 2017) suggesting that MM in isolation provides an alternative, while not superior, treatment approach for treatment-resistant SAD patients.

Next to MM, recent studies have shown that the classical psychedelic psilocybin, a serotonin 2 A receptor agonist, is a promising therapeutic agent in treating affective disorders like depression and anxiety (Reiff et al., 2020). Unlike conventional treatment approaches, psychedelics are administered only a limited number of times in a supportive setting, followed by multiple integration sessions (Johnson and Griffiths, 2017). Previously it was suggested that psilocybin administered during a MM retreat promotes meditation depth during the session and positive changes in psychosocial functioning at a 4-month follow-up (Smigielski et al., 2019) in healthy, experienced meditators. This change was predicted by an acute positively experienced loss of self-identity (ego--dissolution), which was linked to a decoupling of the mPFC and posterior cingulate cortex (PCC) measured post-acutely one day after the 5-day MM retreat. As part of the anterior-posterior default mode network (DMN), these two regions are relevant to the clinical symptoms of SAD (Yoon et al., 2019). Together, this might lead to hypothesize that the positive effects of MM in SAD might be facilitated by concomitant psilocybin administration through complementary effects on brain-regions involved in self-awareness. While similar treatment effects may be achieved through a combination of CBT and psilocybin a comparison would go beyond the scope of this paper and requires an individual analysis.

This qualitative literature review aims to investigate whether the combination of MM and psilocybin can theoretically be considered as a potentially successful treatment for SAD based on their effects on brain activity and connectivity given what is currently known about brain anomalies in SAD. To answer this question, the effects of MM and psilocybin on neural mechanisms showing anomalous activation patterns in SAD patients compared to control groups when confronted with socially fearful stimuli will be reviewed. The model presented in Fig. 1 will be used as a framework to review the findings.

2. Methods

2.1. Literature search strategy

This qualitative, systematic literature review was performed following the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (Moher et al., 2009). The search was performed via the search engine PubMed in January 2021. To identify relevant literature concerning the neurological mechanisms underlying mindfulness meditation and psilocybin treatment, two separate search strings were applied. For the search string of meditation, the key terms "Mindfulness meditation, Neuronal Activity, Networks, Brain imaging, Tomography" were used. The second search string entailed the keywords "Psilocybin, LSD, Neural activation, brain imaging, nuclear, tomography, fMRI". LSD was included in this search as it has similar subjective effects and mechanisms of action to psilocybin and is considered to play a role in social processing (Schmid and Liechti, 2018). Therefore, it may warrant additional insight into therapeutic mechanisms relevant to SAD. Further literature relevant to this topic was identified based on citations from included studies.

2.2. Study selection and data extraction

The literature search for this review was limited to clinical trials published in English. Article titles and abstracts were screened and selected based on the following criteria: (1) published in a peer-reviewed journal, (2) assessing the effects of Psilocybin/LSD or MM, and (3) neuroimaging was performed with fMRI. Studies using other neuroimaging techniques were not included to avoid discrepancies resulting from differences in the method of analysis as previously demonstrated following emission tomography (PET) research compared to arterial spin labeling (ASL) (Lewis et al., 2017). Studies that only investigated constructs related to the psychological factors of the model and did not including an imaging component were not included in this review. This might limit the body of supportive evidence of combined psilocybin-mindfulness meditation therapy in SAD. The reader should be aware of the focus on neurobiology in the present review.

3. Results

A flow chart depicting the selection and review process is shown in Fig. 2. The search performed via the search engine PubMed in January 2021 yielded 112 search results. One article was removed as a duplicate from the two search strings (n = 111). Screening of titles and abstracts based on the aforementioned exclusion criteria resulted in the inclusion of 35 articles. An extended evaluation led to the exclusion of 11 articles of which one was removed as the research sample included bipolar

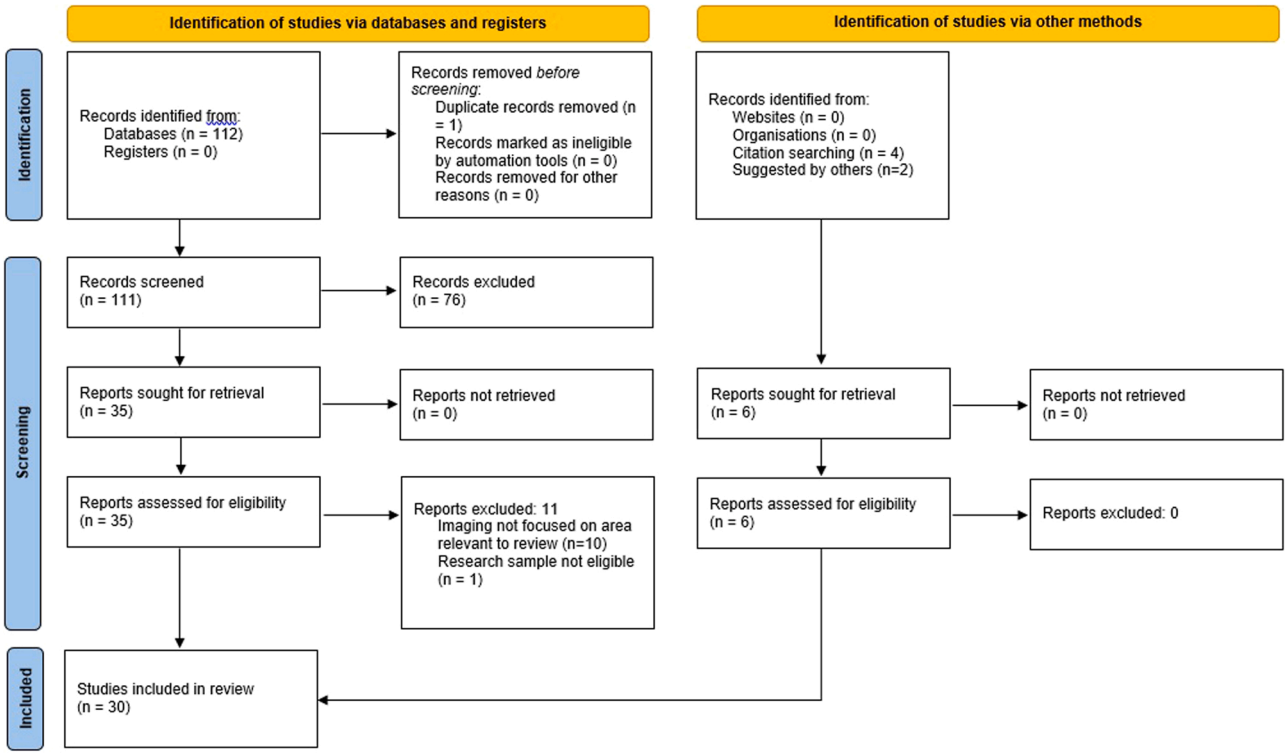

Fig. 2. Flow chart of the selection and review process that resulted in the inclusion of 28 articles in the current review.

disorder patients, and 10 articles were removed as the discussion was focused on neurological structures that were not relevant to the neural correlates of SAD defined in the introduction of this paper (n = 24). Six relevant records were added of which four were added based on citations from the included articles and two records were included based on suggestions by others. Finally, this resulted in including 30 articles as a database for the analysis.

The majority of studies assessed the effect of psilocybin or MM in a healthy sample. Four studies included in this review are based on a clinical sample. More specifically, two studies focused on participants with treatment-resistant depression, one focused on participants with SAD, and one focused on participants with breast cancer. Eleven studies assessed psychedelic effects through the administration of psilocybin and six studies through the administration of LSD. Most studies could be linked with five factors of the model for which brain anomalities in SAD are known including biased attention towards social threats, self-focused attention, self-perception, cognitive/emotional control and post-event rumination. No clear neurobiological evidence in SAD exists yet on the other factors mentioned in Fig. 1. A summary of the main findings is presented in Table 1.

3.1. *The effects of psilocybin and MM on brain activation and connectivity*

The effects of psilocybin and MM on neural processes are discussed as stated per psychological factor of the model for which evidence was available; this is then integrated into the model and presented in Fig. 3.

3.1.1. *Effects of psilocybin and MM on biased attention towards social threats*

Patients affected by SAD have a biased attention towards social threats, which can reinforce itself following subsequent social encounters and thereby intensify the pathology of SAD (Hofmann, 2007). Previously, it has been shown that this is linked with increased activity of the anterior insula which is together with the dorsal anterior cingulate cortex part of the salience network (SN). Other subcortical nodes which are part of the amygdala, hypothalamus, ventral striatum, and the thalamus are incluced in the SN too. Additionally aberrant FC of the SN was shown too. When reviewing the imaging studies with psychedelics and MM, we identified nine studies that showed changed activity or connectivity in these brain areas and networks too.

Carhart-Harris et al. (2012) mapped the effects of intravenously administered psilocybin (2 mg) in healthy volunteers versus placebo during resting-state imaging. Their findings suggest an acute decrease of activation, which was maximal in regions including the thalamus, ACC, PCC, and mPFC; there was also a decrease in the positive coupling between the mPFC and PCC. The authors stated that this effect pattern can enable a state of unconstrained cognition, not hampered by filters or biases, which is the opposite in SAD. The link between the study by Carhart-Harris et al. (2012) and the brain areas shown to be involved in biased attention in SAD is the ACC which is part of the SN. Furthermore, psilocybin (2 mg, i.v.) increased the connectivity between two otherwise orthogonally networks, the DMN and the task-positive network (TPN) in healthy volunteers during resting state imaging. This indicates the reduction of the separateness of the internal and external focus, something that is also observed in meditative states (Carhart-Harris et al., 2013). In the context of the proposed model, this might mean that the activity of the SN, which serves as a switch between the DMN (introspection) and the TPN (externally focused attention) is disturbed by psilocybin, which is partly confirmed by the increased FC between the DMN and the SN after psilocybin administration and the hypoconnectivity in the insula (part of the SN) as shown by Preller et al. (2020) after oral administration of 0.2 mg/kg psilocybin. Müller et al. (2018) investigated resting state activity in healthy volunteers after oral administration of 100 μg LSD compared to placebo. They demonstrated a decrease in within FC of several networks including the DMN and an increase in FC between all networks. Relevant for our model is the increase in connectivity between networks and the ACC, striatum, and the thalamus, which are all part of the SN (Müller et al., 2018). While the SN as such was not part of the analysis, it is partly in line with Carhart-Harris et al. (2013) showing increased FC between the DMN and the SN. Tagliazucchi et al. (2016) showed increased connectivity between

Table 1
Overview of experimental studies included in the review.

Study	Sample	Design/Intervention	Construct (measure)	Findings
Allen et al. (2012)	Healthy participants, no previous experience (N = 61)	BS, 2 groups, 6-week MT, active control	Error-awareness task, fMRI during affective Stroop task	↑dorsolateral PFC response during executive processing ↑dorsal ACC, MPFC, right anterior insula during negative valence processing
Brewer et al. (2011)	Healthy adult participants (N = 25)	BS, LTM (average 10.565 ± 5.148 h MM experience), MNP	fMRI during meditation and resting-state	↓ activity in PCC and mPFC in LTM ↑ FC between PCC, dACC and dlPFC in LTM (baseline and during meditation)
Creswell et al. (2007)	Healthy participants (N = 27)	BS, PPs ordered along MAAS (dispositional mindfulness) scores	fMRI during affect labeling/control task	↑widespread prefrontal cortical activation during affect labeling ↓bilateral amygdala activity during affect labeling
Doll et al. (2016)	Healthy participants, no previous experience (N = 26)	WS, 2-week mindfulness-based attention-to-breath (ATB) meditation	Affect ratings, Respiration measures, fMRI while viewing aversive pictures (passive viewing vs attention-to-breath)	↑ left DMPFC related to ATB ↑ fronto-parietal network during emotion stimulation ↓amygdala activation ↑amygdala-prefrontal integration
Doll et al. (2015)	Healthy participants, no previous experience (N = 26)	BS, 2-week daily attention-to-breath mediation	Resting-state fMRI, compared based on mindfulness score	↑inter-network intrinsic FC between subnetworks of the DMN and DN ↑inter-network intrinsic FC between subnetworks of SN and CEN
Garrison et al. (2015)	Healthy adult participants (N = 46)	BS, LTM (average 9.676 ± 1.586 h MM experience), MNP	fMRI during meditation, active cognitive task (judgement of adjectives task) and resting-state	↓ activation of DMN during mediation for LTM (PCC/precuneus and ACC)
Goldin and Gross (2010)	SAD patients (N = 14)	WS, pre- 8 week MBSR, post- 8 week MBSR	fMRI during emotion regulation task (breath-focused attention vs distraction-focused attention)	↓ amygdala activity ↑activity in regions of attentional deployment (inferior and superior Parietal lobe, cuneus, precuneus, middle occipital gyrus)
Kral et al. (2018)	Healthy Participants (partly LTM) (N = 151)	BS, 3 groups, LTM, MNP receiving 8-week MSBR intervention or active control (HEP)	FFMQ, Automatic emotion regulation task during fMRI	↓ right amygdala activation during positive pictures ↑ FC Amygdala-VMPFC
Kilpatrick et al. (2011)	Healthy, meditation-naïve women (N = 32)	BS, 8-week MBSR-training, waiting period	fcMRI during focused attention task	↑FC within auditory and visual networks ↑FC between auditory cortex and salience ICN (dACC) and anterior DMN (dmPFC) ↑differentiation between auditory and visual networks ↑differentiation between visual and salience ICN (sACC) and anterior DMN (dmPFC)
Monti et al. (2012)	Breast cancer patients (N = 18)	BS, 8-week MBAT, active control	fMRI, during rest, meditation, and stress task	↑CBF at rest and meditation in left insula, right amygdala, right hippocampus, and bilateral caudate ↓activation in posterior cingulate (stressful cue)
Taren et al. (2017)	Healthy, elevated psychological distress (N = 35)	BS, 3-day HEM, HER (active control)	Resting-state fMRI	↑ rsFC between dlPFC and dorsal network regions (superior parietal lobule, SEF, MFG) ↑rsFC between dlPFC and ventral network regions (right IFG, middle temporal/angular gyrus)
Taylor et al. (2013)	Healthy adult participants (N = 24)	BS, LTM (average 6.519 ± 14.445 h), MNP	fMRI during resting-state	↓ FC of dmPFC with left IPL and vmPFC and vmPFC with right ITC ↓FC between left IPL and PCC ↑ FC of right IPL with dmPFC, left IPL and PCC
Zeidan et al. (2011)	Healthy adult Participants (N = 15)	WS, pre-post 4-day MM training for pain reduction	Arterial spin labeling fMRI	↑ activity in ACC and anterior insula ↑ activity in OFC ↓ Thalamic regions
LSD and psilocybin studies				
Barrett et al. (2020)	Healthy participants (N = 12)	WS, 1-d before, 1-w post, 1-m post psilocybin administration (25 mg/70 kg p.o.)	fMRI during rest and completion of 3 emotion processing tasks (emotion discrimination, emotion recognition, emotional conflict stroop task)	↓ Amygdala response to emotional stimuli 1-week post-psilocybin (rebound at 1-month post) ↑ dlPFC and MOC to emotional stimuli 1-week post-psilocybin (1 month?) ↑ global FC at 1-week and 1-month post-psilocybin
Bernasconi et al. (2014)	Healthy participants (N = 30)	WS, placebo and psilocybin (170 μg/kg p.o.) (separated by 2 weeks)	EEG during passive-viewing emotional face task	↓ response in amygdala, parahippocampal gyrus, and right temporal cortex for neutral and fearful faces ↓response right lingual gyrus, fusiform gyrus, middle-inferior occipital gyrus, bilateral limbic areas, temporoparietal cortices for happy faces
Carhart-Harris et al. (2012)	Healthy, hallucinogen experienced participants (N = 30) (15 ASL and 15 BOLD)	BS, placebo vs. psilocybin (2 mg i.v.)	Resting-state ASL fMRI or BOLD fMRI and FC analysis	↓ cerebral blood flow and BOLD signal strongest in thalamus, ACC, PCC and mPFC ↓ positive coupling between mPFC and PCC

(*continued on next page*)

Table 1 (*continued*)

Study	Sample	Design/Intervention	Construct (measure)	Findings
Carhart-Harris et al. (2013)	Healthy participants with previous psychedelic experience (N = 15)	WS, placebo (i.v. 10 mL saline) and psilocybin (i.v. 2 mg dissolved in 10 mL saline)	fMRI during task-free resting-state	↑increased DMN-TPN FC
Carhart-Harris et al. (2016)	Healthy participants with previous psychedelic experience (N = 20)	BS, placebo vs. LSD (75 μg i.v.)	Resting-state ASL, BOLD and MEG analysis	↑Visual cortex CBF, FC in primary visual cortex ↓FC parahippocampus and retrosplenial cortex, DMN FC
Carhart-Harris et al. (2017)	Patients with diagnoses of treatment resistant MDD (N = 16)	WS, Pre (baseline) and post (1-day after) treatment with psilocybin (2 doses: 10 mg, 25 mg p.o., one-week apart)	Arterial spin labelling (ASL) and resting state fMRI	↓ CBF in temporal cortex including amygdala, post-treatment ↑ rsFC within DMN, post-treatment ↑vmPFC-bilateral inferior parietal cortex rsFC ↓parahippocampla-PFC rsFC
Duerler et al. (2020)	Healthy Participants (N = 24)	WS, placebo, LSD (100 μg p.o.), ketanserin and LSD (40 mg + 100 μg p.o.)	fMRI during social adaptation task	↑mPFC activity during social feedback
Grimm et al. (2018)	Healthy Participants (N = 18)	WS, placebo and psilocybin (0.16 mg/kg, p.o.)	Event-related face discrimination task	↓ FC during happy and angry face stimuli vs neutral between left striatum and right amygdala (angry) and right amygdala and medial frontal pole (happy)
Kraehenmann et al. (2015)	Healthy participants (N = 25)	WS, placebo and psilocybin (0.16 mg/kg p.o.)	fMRI while completing modified version of amygdala reactivity task (picture discrimination task)	↓ (right) Amygdala reactivity to negative and neutral stimuli
Mertens et al. (2020)	Patients diagnosed with treatment-resistant depression (N = 19)	WS, Psilocybin treatment (25 mg p. o.)	fMRI during classic face/emotion perception task	↓FC of vmPFC – right amygdala during face processing post- (versus pre-) treatment ↑FC between amygdala and vmPFC to occipital-parietal cortices during face processing
Mueller et al. (2017)	Healthy participants (minimal lifetime exposure to illicit drugs) (N = 20)	BS, Placebo or LSD (100 μg p.o.)	fMRI during affective face paradigm	↓ reactivity of left amygdala and right mPFC
Müller et al. (2018)	Healthy participants (N = 20)	BS, placebo, or LSD (100 μg p.o.)	Resting-state fMRI	↓ FC within visual, sensorimotor, auditory, and DMN network ↑ FC between networks ↑connectivity between networks and subcortical (thalamus, striatum) and cortical (precuneus, ACC) hub structures
Preller et al. (2016)	Healthy participants (N = 21)	WS, placebo and psilocybin (0.215 mg/kg p.o.)	fMRI during social exclusion + resting state MRS	↓ response to social exclusion in dACC and middle frontal gyrus
Preller et al. (2018)	Healthy participants (N = 24)	WS, placebo, LSD (100 μg p.o.), LSD + Ketanserin	Eye-tracking and fMRI during self- and other-initiated joint and non-joint attention tasks	↓ activity in brain areas important for self-processing and social cognition (PCC and angular gyrus) ↓ activity in mPFC
Preller et al. (2020)	Healthy participants (N = 23)	WS, placebo and psilocybin (0.2 mg/kg, p.o.)	Resting state FC over 3 timepoints (20, 40 and 70 min post-treatment)	Hypoconnectivity in subcortical areas and bilateral areas (e.g., mPFC, lPFC, cingulum, insula, temporoparietal junction) Hyperconnectivity in sensory areas (specifically the bilateral occipital cortex)
Smigielski et al. (2019)	Healthy, experienced meditator participants (N = 38)	BS, psilocybin (315 μg/kg p.o.) or placebo	fMRI, pre- and post-intervention (5-day mindfulness retreat + psilocybin (315 μg/kg /placebo)	↑ rsFC antero-ventral DMN ↓ FC of antero-posterior DMN during open awareness (mPFC and PCC)
Tagliazucchi et al. (2016)	Healthy, psychedelic experienced participants	BS, placebo and (i.v. 10 mL saline), LSD (i.v. 75 μg in 10 mL saline)	fMRI during eyes-closed resting-state	↑global integration within brain ↓within-module integrity

Abbreviations: BS= Between subject; WS= within subject; LTM= long-term mediator; MNP= Meditation-naïve participant; HEP= Health Enhancement program; HEM= Health Enhancement through Mindfulness= MBSR= Mindfulness Based Stress Reduction; VMPFC= ventromedial prefrontal cortex; DMPFY= dorsomedial prefrontal cortex; MT= mindfulness training; DLPFC= dorsolateral prefrontal cortex; ACC= anterior cingulate cortex; PP= Participants; MAAS= Mindful Attention Awareness Scale; BPD= Bipolar Disorder; MBCT= mindfulness-based cognitive therapy; PCC= posterior cingulate cortex; FC= functional connectivity; ICN= intrinsic connectivity networks; DMN= default mode network; sACC= supragenual anterior cingulate cortex; MBAT= Mindfulness-based Art Therapy; CBF= cerebral blood flow; RR= relaxation response; SMA= sensory motor area; IBMT= integrative body-mind training; RT= relaxation training; HEM= Health Enhancement through Mindfulness; HER= Health Enhancement through Relaxation; SEF= supplementary eye fields; MFG= middle frontal gyrus; IFG= inferior frontal gyrus; MCI= mild cognitive enhancement; OFC= orbital frontal cortex; rsFC= resting-state functional connectivity; MOC= medial occipital cortex; TPN= task-positive network; ASL= Arterial spin labelling; MDE= 3 = 4-methylenedioxyethylamphetamine; METH= D-methamphetamine; rMRGlu= relative metabolic rate of Glucose; DCM= dynamic causal modeling; 5-HT 2 A= Serotonin 2 A; i.v.= intravenous; p.o. = per os (orally)

higher-level association cortices, overlapping with the DMN, SN, and frontopartietal attentional networks and the thalamus after i.v. administration of LSD (75 μg in 10 mL saline) (Tagliazucchi et al., 2016). Lastly, Barrett et al. (2020) who included both task-related imaging and resting state imaging demonstrated that global resting-state FC in healthy volunteers increased from baseline to both 1-week and 1-month following oral administration of psilocybin (25 mg/ 70 kg). Networks included the DMN, attentional network and the SN. The task-related imaging demonstrated a change in amygdala responsiveness to emotional stimuli; One-week post-psilocybin, this response to a mix of positive and negative stimuli was reduced whereas this returned to baseline one-month post-psilocybin. It was suggested that psilocybin might (transiently) increase emotional and brain plasticity. Next to the longer-lasting effects, other task-based imaging studies have shown that psilocybin (0.16 mg/kg) reduces amygdala activity in when having to discriminate negative facial expressions from neutral (0.16 mg/kg) (Grimm et al., 2018; Kraehenmann et al., 2015).

Whereas the general trend in the reviewed psychedelic imaging

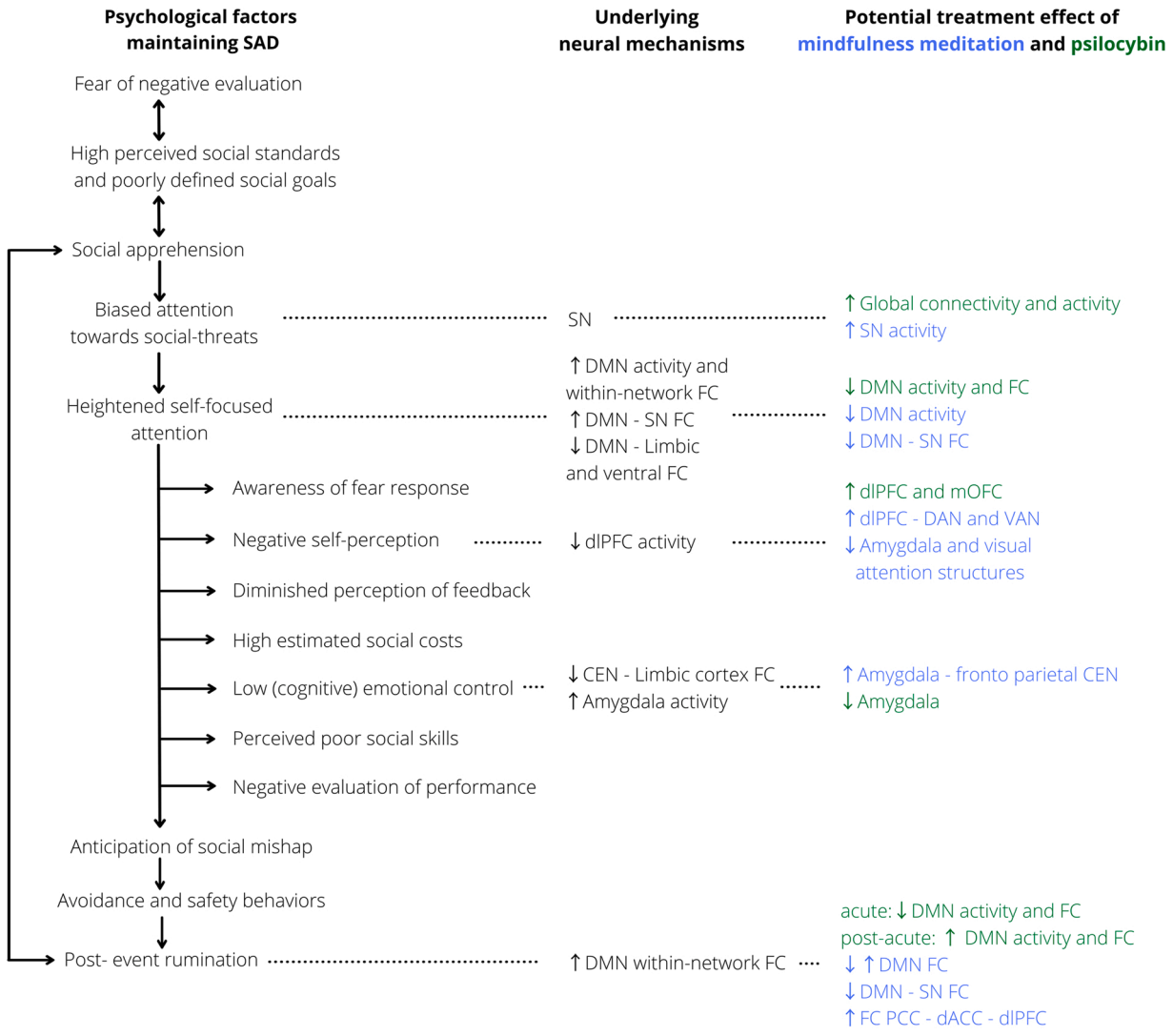

Fig. 3. A model of potential treatment effects of mindfulness meditation (MM) and psilocybin based on neural deviances in social anxiety disorder (SAD); *Abbreviations: SN= Salience Network; DMN= Default mode network; FC= functional connectivity; dlPFC= dorsolateral prefrontal cortex; CEN= central executive network; mOFC= medial orbitofrontal cortex; DAN= dorsal attention network; VAN= ventral attention network; dACC= dorsal anterior cingulate cortex.*

studies was that global connectivity was increased, it might be that MM training alters more specific connections in the brain compared to psilocybin; studies have shown that MM training affects the processing of stimulus salience by increasing activity in the SN. Allen et al. (2012) compared the neural activity of healthy participants engaging in an affective Stroop task after six weeks of MM ('experimental group') or group reading ('control group') training. Participants with high amounts of MM practice showed increased activity of the dorsal anterior cingulate cortex (dACC), mPFC, and anterior insula (AI) in response to emotional stimuli in the Stroop task and reduced affective Stroop conflict compared to the control group. These regions are also active during explicit mindfulness practice, and it was suggested that participants transfer their skill in mindfulness-based attentional control to emotionally challenging situations (Allen et al., 2012). Likewise, Zeidan et al. (2011) reported increased activity in the ACC and AI in healthy participants responding to noxious stimulation during meditation, after a 4-day mindfulness training compared to baseline. This change in activity was correlated to lower pain intensity ratings. Both studies indicate that MM is associated with higher activity in the SN in response to affective or painful stimuli, which interestingly goes in the same direction as seen in SAD.

The reviewed studies (N = 10) in healthy volunteers suggest, that psilocybin and MM seem to show different effects on global network resting state FC and the attention allocation network it has to be noted that the imaging studies with psychedelics included resting state, i.e., in the absence of stimuli, while the MM studies included task-based imaging assessing activity and connectivity during stimulus exposure. It was suggested that psilocybin potentially induces an acute state of flexible cognition by destabilizing global network connectivity, making the distinction between internal and external focus fuzzy. It was even suggested that the connectivity pattern resembles that of meditative states (Barrett et al., 2020; Carhart-Harris et al., 2012, 2013; Müller et al., 2018; Tagliazucchi et al., 2016). The task-based imaging studies showed that psilocybin reduces the amygdala activity acutely up to one-week post-administration when confronted with negative emotional stimuli (Barrett et al., 2020; Grimm et al., 2018; Kraehenmann et al., 2015). MM training seems to improve attention allocation by increasing activity in the SN (Allen et al., 2012; Zeidan et al., 2011); as said, these findings were the result of task-based imaging, when participants were exposed to emotional or noxious stimuli. Based on the neurological mechanisms involved in the symptomology of SAD, it was shown that both psychedelics and MM changes the SN activity or the connectivity of parts of the SN with other networks potentially enabling flexible cognition and reducing attention allocation if confronted with socially

threatening stimuli.

3.1.2. Effects of psilocybin and MM on heightened self-focused attention

Patients with SAD have a heightened self-focused attention compared to healthy controls; this is related with increased DMN activity and within network FC, increased DMN-SN FC, and decreased DMN-limbic and ventral FC. Up to now, three studies have investigated the acute effects of LSD and psilocybin on brain activity in healthy participants while being engaged in social tasks (Duerler et al., 2020; Preller et al., 2016, 2018). Administration of LSD (100 μg, p.o.) compared to placebo during a joint attention task was linked to reduced activity in structures belonging to the DMN (PCC and mPFC) which was suggested to reflect decreased self-referential processing and lowered differentiation between the self and others during social interactions (Preller et al., 2018). Preller et al. (2016) demonstrated decreased activation of the middle frontal gyrus and dACC in response to social exclusion, after administration of psilocybin (0.215 mg/kg, p.o.) compared to placebo in healthy participants (Preller et al., 2016). This significantly correlated to changes in self-referential processing leading the authors to suggest that psilocybin might mitigate the processing of negative social interactions through changes in self-referential processing and the adjustment of activity in the dACC (Preller et al., 2016). In contrast, after administration of LSD (100 μg, p.o.), participants showed increased activity in the mPFC in response to social feedback compared to placebo (Duerler et al., 2020). The increase of mPFC activity was specific to social feedback processing and not observed during social decision making, which suggests that LSD may increase the value assigned to the opinion of others via effects on self-relevance processing. For this latter effect, it might be debatable what this would mean for SAD patients who already fear the opinion of others; however, the fact that the difference between the self and the other is reduced, this might mean that they do not feel threatened by the opinion of others, although this is highly speculative.

Accordingly, MM training modulates activity in structures belonging to the DMN. Experienced meditators showed downregulation of the mPFC and PCC activity during resting- and active meditation state compared to meditation naive participants (Brewer et al., 2011; Garrison et al., 2015). Similarly, Monti et al. (2012) reported decreased activity in the PCC in response to stressful cues in breast cancer patients after undergoing 8-week mindfulness-based art therapy compared to patients in an education control group (Monti et al., 2012). Furthermore, Kilpatrick and colleagues (2011) demonstrated decreased FC between the SN (dACC) and the DMN (dmPFC) during a focused attention task in healthy participants after following an 8-week mindfulness-based stress reduction (MBSR) program compared to a waiting list control condition (Kilpatrick et al., 2011). This decrease in connectivity was linked to lower levels of mind wandering during task engagement. In summary, the findings indicate that MM might decrease focus on self-related processing during rest, meditation, focused attention, and in response to stress-provoking cues.

Taken together, the reviewed evidence (N = 7) suggests complementary effects of psilocybin and meditation reducing the focus on self-referential processing during active engagement in social tasks (Brewer et al., 2011; Duerler et al., 2020; Garrison et al., 2015; Kilpatrick et al., 2011; Monti et al., 2012; Preller et al., 2016, 2018). Both treatments decrease activity in the medial structures of the DMN (PCC and mPFC) (Monti et al., 2012; Preller et al., 2018). Additionally, acute effects of psilocybin reduced activity in the dACC (Preller et al., 2016) while MM decreased the connectivity between the dACC (SN) and the dmPFC (DMN) (Kilpatrick et al., 2011). As heightened self-focused attention was linked to increased activity of the DMN and functional connectivity with the SN this might suggest social feedback processing and self-focused attention in SAD patients as potential treatment target.

3.1.3. Effects of psilocybin and MM on negative self-perception

Delayed automatic activation of the dlPFC in response to anxiety-provoking social situations has been linked to delayed control over negative self-beliefs in SAD patients, facilitating negative self-perception generation (Goldin et al., 2009). In healthy participants, administration of psilocybin (25 mg/70 kg, p.o.) has led to increased recruitment of the dlPFC and medial orbitofrontal cortex (mOFC), while decreasing amygdala reactivity in response to emotional faces (happy, neutral, and fearful) at 1-week post-psilocybin compared to baseline (Barrett et al., 2020). This increased activation of the dlPFC and mOFC was suggested to reflect greater recruitment of cognitive decision-making circuits involved in the downregulation of automatic emotional responses.

Likewise, MM training was shown to affect the cognitive control networks. During resting-state, findings indicated increased FC between the dlPFC (CEN) and structures of the dorsal (DAN) and ventral (VAN) attention network in adults with elevated levels of psychological distress following a 3-day intensive mindfulness training compared to relaxation training (Taren et al., 2017). Goldin and Gross (2010), who investigated the effects following an 8-week MBSR program on negative self-beliefs in SAD patients, demonstrated reduced activity in the amygdala. In contrast, activity in regions involved in visual attention allocation, including the inferior and superior parietal cortex, cuneus, precuneus, and the middle occipital gyrus, was increased. These findings were associated with decreased SAD symptoms, suggesting that patients improved visualizing their negative self-beliefs instead of applying avoidance strategies while keeping control over their fear response following improved implicit attentional control (Goldin and Gross, 2010). Further, the findings indicated decreased behavioral SAD symptoms and improved mental well-being of patients.

To conclude, based on the studies reviewed (N = 3), psilocybin and MM might show complementary effects to persistently increase cognitive control over automatically generated negative self-beliefs (Barrett et al., 2020; Goldin and Gross, 2010; Taren et al., 2017). Consequently, MM training enables more vivid visualization of negative beliefs while controlling automatically generated fears (Goldin and Gross, 2010). The findings suggest that psilocybin and MM affect structures belonging to the attention networks which might be involved in the lack of control over automatic negative self-beliefs in SAD patients. Accordingly, it is hypothesized that psilocybin and MM could reduce negative self-perception in SAD patients.

3.1.4. Effects of psilocybin and MM on brain regions involved in low perceived emotional control

Patients with SAD are know to experience low perceived emotional control, something that is associated with decreased FC between CEN and the limbic cortex, and they also show increased amygdala activity. Imaging studies with psilocybin, showed that emotional processing was altered in healthy volunteers; amygdala reactivity to affective stimuli was reduced during the acute drug effects compared to pre-treatment. This effect appears to be consistent in response to neutral and fearful or negative facial stimuli after administration of psilocybin (160–170 μg/kg, p.o) (Bernasconi et al., 2014; Kraehenmann et al., 2015) and for fearful facial stimuli after administration of LSD (100 μg, p.o.) (Mueller et al., 2017). Further, decreased amygdala reactivity was persistent at one week after psilocybin administration (25 mg/70 kg, p.o.) which suggests that the neurological changes outlast acute drug effects (Barrett et al., 2020). Opposing effects have been reported following psilocybin treatment in a clinical sample with treatment-resistant depression. Amygdala reactivity was increased while processing fearful and happy faces post-psilocybin treatment (10 and 25 mg, p.o.) compared to baseline. Authors suggested that this was proposed to represent reactivation of emotional responsiveness in depressed patients (Roseman et al., 2018; Mertens et al., 2020).

MM training seems to reduce amygdala reactivity to affective stimuli by increasing coupling with prefrontal regions generating increased cognitive control over emotion responses (Creswell et al., 2007; Doll et al., 2016; Kral et al., 2018). Kral et al. (2018) investigated differences in neural activation reactivity to affective pictures between healthy

long-term meditators (LTM) and meditation naïve participants (MNP). Additionally, MNPs following an 8-week mindfulness-based stress reduction (MBSR) were compared to an active control condition receiving a health enhancement program (HEP). The findings indicate increased FC between the PFC and the amygdala and decreased amygdala reactivity to positive stimuli in long-term meditators and MNP after MBSR training. It was suggested that MM training improves emotion regulation strategies, thereby downregulating emotional reactivity (Kral et al., 2018). Decreased reactivity of the amygdala was also reported by Creswell et al. (2007) during affect labeling of facial expressions in participants scoring high versus low in trait levels of mindfulness. This was supported by Doll et al. (2016), reporting reduced amygdala reactivity to aversive (fearful) pictures following a 2-week mindfulness-based attention-to-breath meditation program. Further, the program was associated with increased involvement of a frontoparietal network in emotion regulation comprising lateral and medial parietal regions and superior temporal and medial parts of the ACC (Doll et al., 2016). Together the findings indicate improved cortico-limbic emotion regulation following a mindfulness-based intervention via increased activity of frontoparietal executive control over the amygdala.

Based on the reviewed evidence (N = 7), psilocybin and MM are hypothesized to lead to potential downregulation of activity in the amygdala (Barrett et al., 2020; Bernasconi et al., 2014; Creswell et al., 2007; Doll et al., 2016; Kraehenmann et al., 2015; Kral et al., 2018; Mueller et al., 2017). Whether the combined effect of psilocybin and MM on the amygdala's overly expressed fear response and improve emotional control in SAD patients is synergistic or additive is something that will have to be investigated.

3.1.5. Effects of psilocybin and MM on brain regions involved in post-event rumination

Following a social event, a person with SAD often experiences post-event rumination linked to increased connectivity between the main structures of the DMN during rest. As indicated earlier, during the acute psychedelic state following psilocybin (2 mg, i.v.) or LSD (75–100 μg, p.o.) administration, studies have reported decreased activity and FC within the DMN in healthy participants at rest (Carhart-Harris et al., 2012, 2016; Müller et al., 2018). In comparison, in patients diagnosed with treatment-resistant depression, the resting-state FC within the DMN was increased one-day post- compared to pre- psilocybin treatment (10–25 mg, p.o.) (Carhart-Harris et al., 2017). Mertens et al. (2020) indicated decreased FC between the vmPFC and right amygdala in response to fearful and happy faces in patients diagnosed with treatment-resistant depression following psilocybin-treatment (25 mg, p.o.). These changes correlated with the level of rumination one week post-treatment.

MM training might also alter post-event rumination via effects on the FC of the DMN. Doll et al. (2015) indicated decreased intrinsic FC between the DMN and SN during resting-state, which correlated with mindfulness scores in healthy participants after a 2-week mindfulness-based attention-to-breath training. The authors suggest that this change in connectivity is associated with the ability to attend to the current experience without judgement. We suggest that the decreased connectivity between the SN ('CEN-DMN switch') and the DMN might reduce the focus on self-related thoughts normally leading to post-event rumination. The effects of MM training on FC within the DMN were investigated by Taylor et al. (2013), comparing experienced meditators with MNP during rest. They showed that experienced meditators have weaker FC between DMN regions involved in emotional appraisal; stronger FC was reported between the right parietal cortex with the dmPFC, the left IPL, and the PCC/precuneus (Taylor et al., 2013). Reduced coupling between the right parietal cortex and the precuneus has previously been associated with self-referential processing. As this connection was strengthened in experienced meditators, it was suggested that MM can lead to a reduction in self-referential processing during rest and increments in present-moment awareness. Increased FC with the DMN (PCC, dACC, and dlPFC) in experienced meditators at rest was positively correlated with decreased mind-wandering as reported by Brewer et al. (2011).

A recent study that investigated the effect of psilocybin (315 μg/kg, p.o.) compared to placebo in experienced meditators during a mindfulness retreat showed decoupling of the mPFC and PCC one day post psilocybin administration. While these structures are associated with mediating a sense of self, the observed post-acute decoupling correlated positively with the subjective experience of ego-dissolution during the psilocybin-assisted mindfulness session. Four months after the psychedelic experience, the extent of ego-dissolution and network connectivity changes could predict improvements in psychosocial functioning (Smigielski et al., 2019). The observations suggest that psilocybin, combined with meditation, affects the neurological network underlying self-referential processing.

The evidence reviewed (N = 9) suggests that psilocybin administration and MM training reduce self-referential processing during resting states While psilocybin has been proposed to induce acute disintegration of the DMN, MM training might improve functional control over DMN activity (Brewer et al., 2011; Carhart-Harris et al., 2012; Carhart-Harris et al., 2016; Carhart-Harris et al., 2017; Doll et al., 2015; Mertens et al., 2020; Müller et al., 2018; Smigielski et al., 2019; Taylor et al., 2013). These findings suggest that psilocybin and MM both affect the DMN, which has been linked to rumination in SAD patients. Accordingly, psilocybin might enable acute detachment from thoughts while MM training seems to improve control over mind wandering and rumination.

3.2. A comprehensive model on the effects of psilocybin and MM on neural mechanisms relevant to psychological symptoms of SAD

Based on the reviewed evidence, Fig. 3 proposes a model integrating the effects of psilocybin and MM on the mechanisms maintaining SAD.

In this review, five psychological factors maintaining SAD based on the model by Hofmann (2007) have been linked to anomalies in the DMN, SN, CEN, and the limbic system. To identify potential treatment mechanisms for SAD, the reviewed findings on the effects of MM (blue) and psilocybin (green) have been linked to these neural mechanisms. It becomes apparent that MM and psilocybin might be able to act synergistically on several structures and mechanisms involved in SAD symptoms. It is suggested that psilocybin-assisted mindfulness-based intervention is a promising future treatment for SAD patients.

4. Discussion

Social anxiety disorder impairs many patients' social interactions and reduces their general quality of life. Therefore, this review investigates whether a treatment combining psilocybin and MM could generate beneficial therapeutic effects via alterations in neural networks that show anomalous activity in SAD compared to healthy controls. The findings presented in this review suggest that both treatments alter neural processes underlying the symptoms of SAD and might be complementary in their effects. However, psilocybin and MM show considerable differences in how they act and might alter the neural mechanisms underlying SAD.

The findings indicate that a single dose of psilocybin (fixed dose: 10, 25 mg; weight-based dose: 11.2–25 mg/70 kg) might cause an acute disintegration of neurocognitive networks by inducing globally increased activity and connectivity between networks which was associated with the experience of unconstrained cognition (Carhart-Harris, Erritzoe et al., 2012; Carhart-Harris et al., 2013; Müller et al., 2018; Tagliazucchi et al., 2016). Further, the literature suggests that psilocybin might cause decreased activity in the DMN while inducing an acute disintegration of the DMN by decreasing within-network connectivity which was positively correlated to the experience of ego-dissolution (Carhart-Harris, Leech et al., 2012; Carhart-Harris et al., 2016; Müller et al., 2018). Ego-dissolution was proposed as an important mechanism

for the improvement of pathological symptoms (Nichols et al., 2017; Johnson and Griffiths, 2017). Findings also showed that psilocybin administration leads to increased recruitment of the dlPFC and mOFC while activity in the amygdala is suppressed in response to affective stimuli, with the latter effect lasting up until one week post-psilocybin administration (Barrett et al., 2020), suggesting a state of emotional and brain plasticity outlasting the acute psychedelic state.

Regarding MM studies, findings show that MM intervention (training program: 3 days-8 weeks; LTM previous experience 6.5–10.6 hrs) modulates the functioning of the SN by increasing activity in the ACC and AI which are proposed to improve attention regulation (Allen et al., 2012; Zeidan et al., 2011). Further, the findings suggest that MM interventions increase the FC between the dlPFC and brain networks involved in attention allocation (Taren et al., 2017) which was previously suggested to increase top-down control over attention and emotion regulation (Tops and Boksem, 2011). The studies discussed in this review show that MM training causes reduced amygdala reactivity to affective stimuli by increasing coupling with prefrontal regions suggesting improved emotional control (Creswell et al., 2007; Doll et al., 2016; Kral et al., 2018). Similar to psilocybin, MM training reduces activity in structures belonging to the DMN but MM also decreases the connectivity between the dACC (SN) and the dmPFC (DMN) associated with lower levels of mind wandering (Kilpatrick et al., 2011).

Accordingly, the synergistic effects of psilocybin and MM on the DMN provide potential support for a combined treatment approach. Previously, alteration in DMN activity involved in self-referential processing was associated with SAD symptom improvement following conventional treatment (Yoon et al., 2019). Hence, this review suggests that psilocybin and MM might exert similar treatment mechanisms to reduce self-focused attention. Decreased focus on self-referential processing during social interactions might enable SAD patients to observe feedback and perceive their performance in a more realistic manner. Automatic generation of negative beliefs has been associated with delayed automatic activation of the dlPFC in SAD while the amygdala is excessively activated in response to affective stimuli. Psilocybin and MM might exert complementary effects on the frontoparietal control network and reduce amygdala reactivity to social stimuli. Therefore, the review proposes that combined effects could improve emotional control and reduce the automatic generation of negative beliefs supporting the idea that the combination of psilocybin and meditation could provide beneficial therapeutic effects. Following a positive treatment outcome, patients can regulate their focus on self-related thoughts, negative self-beliefs and improve their perceived emotional control. Ultimately, patients might experience social interactions as a success and thus experience less post-event rumination. As post-event rumination in SAD has been linked to increased FC within DMN structures this review proposes that psilocybin and MM might support SAD patients to detach from ruminating thoughts. In sum, findings give reason to believe that psilocybin induces instability in overall network connectivity and disintegration of the DMN. Previously, it was hypothesized that the acute decrease of FC of the DMN followed by a post-acute increase may act as a reintegration mechanism and was associated with mood improvements following psilocybin treatment in major depressive disorder (Carhart-Harris et al., 2017). A similar mechanism might produce beneficial treatment effects in SAD but a better understanding of this process is required to support this hypothesis. The findings, as presented in this review and in Fig. 3, offer a rationale for the combined use of psilocybin and MM in the treatment of SAD. Based on these conclusions, several implications for future research are suggested.

4.1. Implications for future research

The findings presented in this review suggest possible synergistic effects of psilocybin-assisted mindfulness-based intervention when treating SAD. In particular, the intervention might improve control over attention allocation, facilitating regulation of negative self-referential processing and emotional control, enabling unbiased perception of social situations. This hypothesis requires experimental research. Ideally, randomized, double-blind, placebo-controlled trials with repeated measurements should assess the effects of psilocybin-assisted mindfulness-based intervention in SAD before drug administration and meditation intervention, during the psychedelic state, the post-acute phase, and at long-term follow-up. To assess treatment efficacy, a focus should be on SAD symptom improvement and previously identified factors, namely emotion control, cognitive and attentional biases, and regulation of negative self-referential processing, including measures such as a clinical diagnostic interview (ADIS-IV) and the Liebowitz Social Anxiety Scale (Liebowitz, 1987). Further, emotion regulation and attention biases might be assessed via responses in aversive picture tasks, comparing reactivity to social and nonsocial threats. To evaluate improvements in self-referential processing, a 'regulation of negative self-belief task' can be used (Goldin, 2010). However, it is advised to add ecologically valid stimuli like situations based on the patient's memory, or to complement the task with ecologically valid measures such as used by Voncken et al. (2021). Here, improvements in social performance were evaluated following a confrontation with live social situations (i.e., a waiting room situation and a getting acquainted task); assessments of post-event rumination could be added.

Until now, there is no explicit consensus regarding the exact procedure, type of psychological support, the dose of the psychedelic, and the number of sessions for psychedelic treatment. What is clear is that the three-phase structure should be implemented, i.e., starting with multiple preparatory sessions, followed by a session with the psychedelic, and multiple integration sessions, guided by two therapists or session monitors to achieve the most significant therapeutic effects and prevent any adverse reactions (Garcia-Romeu and Richards, 2018). The doses used in the included studies are suggested to have therapeutic efficiency based on the effects as mentioned above on SAD-related cognitive processes and neural substrates. Standard mindfulness-based interventions receiving the most empirical support for their efficacy usually involve training sessions over eight weeks (Carmody and Baer, 2009). However, no research has investigated differential effects of MM training before the psychedelic experience and MM training following the psychedelic intervention. Both intervention orders might yield beneficial effects, either preparing for the experience when MM is trained before the psilocybin session, enabling deepened introspection and enhanced ability to focus, or the MM technique might be acquired faster when trained after the psychedelic session when the brain is suggested to show increased reintegration between functional networks (Carhart-Harris et al., 2017). Future research will shed more light on the best practice.

To understand the contribution of each treatment to the treatment effect, different conditions, including placebo and psilocybin sessions with or without MM training, will be instrumental. Also, additional conditions, including SSRIs and CBT as comparators for the psychedelic on the one hand, and the MM therapy, on the other hand, can be considered. Furthermore, as psilocybin-assisted therapy and MM both seem to be promising novel approaches in treating major depressive disorder, it could be particularly promising to investigate treatment efficacy in SAD patients suffering from comorbid depression.

4.2. Limitations

The conclusions discussed in this review study suffer from several limitations. Overall, neuroimaging research with psychedelics and meditation is scarce. The included studies often demonstrate contradictory findings; however, the authors rarely address these contradictions in subsequent research designs and discussions on the findings. In the review process, many methodological differences became apparent between studies, such as diverse assessment methods to measure subjective symptoms and neural changes, something that can affect findings. Findings regarding the effect of MM training might be limited in

their generalizability due to differences in experimental manipulation such as variation in the length of MM training, the type of mindfulness practice, and the experience level of participants (Thomas and Cohen, 2014). Furthermore, several studies did not include an active control group which is essential to conclude effects specific to MM training. While preliminary findings seem very promising, current evidence in psychedelic research is too limited to allow definite conclusions. Consequently, studies are limited to small samples, and very few trials have been executed with clinical patients.

Another point is the debate on the validity and feasibility of placebo conditions in psychedelic research. As the psychedelic state produces substantial psychological effects, participants and therapists could detect whether an active substance was administered (Griffiths et al., 2006). Contrast findings suggest that participants did experience psychological symptoms following placebo administration (Olson et al., 2020). Consequently, further research is necessary to clarify the effects of placebo in psychedelic-assisted therapy, and the need for placebo-controlled trials is highlighted (Gukasyan and Nayak, 2021).

Another issue is that in both research areas (MM and psychedelics) the studies discussed in this review include very different samples. While most studies focused on healthy volunteers, some research has investigated the effects in patients affected by clinical conditions such as major depressive disorder, mild cognitive impairment, and bipolar disorder. The absence of studies in SAD patients should remind us of the caution with which we can conclude about potential treatment efficacy. The focus on neural mechanisms further limits the significance of the present findings. For example, one should not expect a one-to-one overlap between subjective treatment effects and modulation of brain networks, highlighting the importance of future research, including a broad range of neuropsychological measures and neuroimaging techniques.

Lastly, the identification of the relevant studies was based on the proposed neurofunctional model of SAD symptom maintenance; this model might be an oversimplification of actual processes and could have led to disregarding other relevant studies. Despite these limitations, this review proposes a new treatment perspective for patients affected by SAD based on neurofunctional modulations. The proposed model represents possible treatment effects that might guide potential experimental research.

5. Conclusion

This review provides an overview of current scientific literature addressing the effects of mindfulness meditation and psilocybin on brain processes relevant to social anxiety disorder. The findings suggest at least complementary effects on neurological mechanisms implicated in the symptomatology of SAD. Psilocybin seems to cause acute disintegration of core neural networks, subsequently reintegrated in the post-acute phase. During this reintegration process, MM intervention can exert modulatory effects. This is proposed to break the vicious maintenance of SAD by decreasing self-focused attention. Additionally, both treatments appear to alter negative self-perception and emotion regulation via complementary effects on frontoparietal control over the limbic cortex. This review and the proposed treatment model might inspire future research to investigate psilocybin-assisted mindfulness-based interventions as a treatment for social anxiety.

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Declaration of Competing Interest

KK performs company-sponsored and –financed trials with classical psychedelics and empathogens.

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