Specific Aims: Depressive disorders have been identified as a leading cause of disease burden worldwide, and thus constitute a global health problem (Ferrari et al. 2013). In spite of this, there is limited understanding of depression's neurological causes and currently there is no universally effective treatment. Recent research has implicated the dysfunction of a neural network known as the Default Mode Network (DMN) in a variety of psychopathologies (Broyd et al. 2009); in patients with depression, this network appears to be both hyperactive and hyper-connected (Whitfield-Gabrieli and Ford 2012). There is evidence that classical psychedelics reduce the activity and connectivity of the DMN, suggesting that they may have therapeutic value in the treatment of Major Depressive Disorder (MDD). It is hypothesized that the administration of psilocybin to patients with MDD will result in the suppression of DMN activity and connectivity, which will correlate with intensity of subjective drug experience and reduction in depressive symptoms.

The following experiment will be performed on MDD patients. Subjects will be tested initially for DMN activity, connectivity, and anti-correlation with the TPN, as well as for altered consciousness and severity of depression. Half the subjects will receive an oral dose of psilocybin; the other half will receive a placebo. Measurements of DMN activity, connectivity, TPN anti-correlation, and altered consciousness will be made after 2 and 6 hours. Measurements of DMN activity, connectivity, TPN anti-correlation, and severity of depression will be made after 1 day, 2 weeks, 1 month, 3 months, 6 months, and 1 year. Mean changes in DMN measurements and severity of depression will be compared between groups. Within the psilocybin group, individual DMN alterations will be compared with intensity of subjective effects and change in depressive severity.

Significance: The Default Mode Network is a fundamental aspect of human consciousness. DMN activity regulates spontaneous (stimulus-independent) thought and is associated with self-reflective processes, including the formation of judgments about the self, retrieval of memories and contemplation of the future, and the formation of personal beliefs (Whitfield-Gabrieli and Ford 2012). The DMN appears to function in opposition to another brain network, the task-positive network (TPN), and the degree of anti-correlation between these two systems has been shown to significantly predict cognitive ability (Whitfield-Gabrieli and Ford 2012). Beyond MDD, DMN dysfunction has been observed in a variety of psychopathologies, including dementia, schizophrenia, epilepsy, anxiety, autism, and ADHD (Broyd et al. 2009). Therefore, the DMN appears as a critical determinant of cognitive function and mental health. A better understanding of this network may not only elucidate a key cause of mental illness, thus providing new possibilities for treatment, but will also provide essential knowledge about the structure of the human mind. There is experimental evidence that psychedelic drugs alter this network, but the cognitive effects of this alteration as well as the processes by which it occurs are not currently understood. Further research in this area has the potential to reveal the mechanisms by which the DMN is regulated, and thus to provide the means for treating the psychopathologies in which its dysfunction is implicated.

Previous research has identified key aspects of the DMN that are altered in patients with MDD. The DMN is typically thought to include four main regions: the medial prefrontal cortex (mPFC), the posterior cingulate/retrosplenial cortex (PCC/RC), and the left and right inferior parietal lobules (IPLs) (Whitfield-Gabrieli and Ford 2012). These can be functionally divided into anterior and posterior sub-networks, centered

respectively on the mPFC and the PCC (Mulders et al. 2015). Patients with MDD exhibit hyperactivation of both the anterior and posterior DMN during task performance and reduced anti-correlation of the DMN with the TPN (Whitfield-Gabrieli and Ford 2012). Heightened DMN dominance (decreased TPN activity) has been shown to correlate with maladaptive depressive rumination, which is associated with the severity of depressive symptoms (Whitfield-Gabrieli and Ford 2012). Various studies have also identified altered connectivity within the DMN in MDD patients, largely indicating that connectivity within the anterior and posterior sub-networks is increased (Mulders et al. 2015). In particular, heightened connectivity of the subgenual anterior cingulate cortex (sgACC) to the anterior DMN has been correlated with MDD: one study found that the sgACC was not part of the DMN at all in healthy control subjects, but was a prominent part in patients with MDD (Mulders et al. 2015). Furthermore, increased resting-state connectivity between the sg-ACC and the PCC has been observed in MDD patients, and the degree of connectivity was associated with rumination and brooding (Whitfield-Gabrieli and Ford 2012). Increased functional connectivity of the sgACC with the DMN has also been shown to significantly correlate with the duration of depressive episodes (Whitfield-Gabrieli and Ford 2012). There is some evidence that remitted MDD patients show altered DMN connectivity compared to current MDD patients (Qin et al. 2015), suggesting that effective MDD treatment involves DMN normalization. However, there is currently no research that directly examines the therapeutic efficacy of DMN alteration.

Previous research has also established a connection between classical psychedelics and alteration of the DMN. One study (Carhart-Harris et al. 2012) found that psilocybin decreased the activity of several major DMN structures, including the

mPFC/ACC and the PCC. The reduction in mPFC/ACC activity in particular was correlated with the intensity of the subjective effects of the drug. Furthermore, psilocybin decreased the positive coupling of the mPFC/ACC and the PCC. A study (Palhano-Fontes et al. 2015) examining the effects of ayahuasca (a psychedelic compound that increases monoaminergic transmission) similarly found decreased activity in the major DMN structures, specifically the mPFC/ACC, PCC/PC, and the right and left IPLs. Again, reduction in ACC activity most significantly correlated with subjective effects. This study also found a decrease in connectivity within the PCC/PC, but it did not identify a decrease in connectivity between the PCC and the mPFC. This discrepancy, however, may reflect the differential mechanisms by which psilocybin and ayahuasca act. In general, these studies suggest that the effects of psychedelic drugs on the DMN oppose the DMN alterations exhibited by MDD patients. One study (Carhart-Harris et al. 2013), however, found that psilocybin increased correlation between the DMN and the TPN. Because MDD patients exhibit reduced anti-correlation between the DMN and the TPN, this finding seems to suggest that psychedelic drug use would exacerbate, rather than attenuate, MDD severity. However, all of these studies used healthy (non-MDD) subjects, and none of them measured changes in mood.

There is some evidence for psychedelic-mediated mood improvements in healthy subjects as well as in cancer patients (Baumeister et al. 2014). Currently, however, there is no research directly addressing the therapeutic effects of psychedelic drug use on MDD.

Experiment: Subjects will be limited to otherwise healthy adults with Major Depressive Disorder (as defined by the DSM V) who are not currently taking anti-depressants and

who have no previous experience with psychedelic drug use. The study will evaluate the effects of psilocybin on DMN activity, connectivity, and anti-correlation with the TPN. Alterations in DMN functioning will be compared to intensity of subjective effects and changes in depression severity.

Resting-state blood-oxygen level-dependent (BOLD) fMRI will be used to determine DMN activity, functional connectivity, and anti-correlation with the TPN (Carhart-Harris et al. 2012; Carhart-Harris et al. 2013; Palhano-Fontes et al. 2015); subjects will be asked to close their eyes and relax while they are scanned. The Brief Psychiatric Rating Scale (BPRS) and the 5-Dimension Altered States of Consciousness Profile (5D-ASC) will be used to assess intensity of subjective effects (Grob et al. 2011). The Hamilton Rating Scale for Depression (HAM-D) will be used to assess severity of depression (Rosenberg 2000).

Subjects will be randomly divided into two groups: A (control) and B (experimental). At the start of the experiment, subjects will be tested as described above to establish initial results. Psilocybin and placebo will be administered orally in pill form. Psilocybin has been chosen because of its previous use in studies of DMN alteration (Carhart-Harris et al. 2012; Carhart-Harris et al. 2013) and therapeutic applications (Baumeister et al. 2014). Psilocybin will be dosed at 0.2 mg/kg; this is considered a moderate dose and has previously been found to be therapeutic (Grob et al. 2011). Placebo will be niacin (250 mg), which creates a mild physiological reaction but does not affect psychological state (Grob et al. 2011)

Subjects will undergo fMRI, BPRS, and 5D-ASC tests 2 hours after administration, at which peak physiological responses (heart rate and blood pressure

increases) to psilocybin have previously been observed, and 6 hours after administration, at which effects should be subsiding (Grob et al. 2011). Subjects will return for follow-up tests (fMRI and HAM-D) after 1 day, 2 weeks, 1 month, 3 months, 6 months, and 1 year; previous work with psilocybin has shown lasting effects at 6 months (Baumeister et al. 2014).

DMN activity will be assessed using spatial independent component analysis (sICA) of resting-state fMRI; sICA maps functional brain networks (van de Ven et al. 2004). DMN connectivity and DMN-TPN anti-correlation will be determined using seed-driven analysis of resting-state fMRI. Seed-driven analysis reveals functional connectivity between a selected region of interest (seed) and other brain regions (Cohen et al. 2008). For connectivity analysis, selected seeds will be the mPFC and PCC, because of their centrality, respectively, to the anterior and posterior DMN (Palhano-Fontes et al. 2015), as well as the ACC, because of its established involvement in MDD and its hypothesized involvement in subjective psychedelic effects. For DMN-TPN anti-correlation, a ventromedial PFC (vmPFC) seed-based analysis will be used to define the DMN (vmPFC-positive network) and TPN (vmPFC-negative network) and assess changes in connectivity between the two (Carhart-Harris 2013).

There are several potential problems with this experimental design. Niacin has previously been found to be largely ineffective as a placebo (Grob et al. 2011), and it seems likely that even psychedelic-naïve subjects will be able to discriminate between the two, given niacin's lack of psychological effects. However, any placebo that did alter psychological state would not be an effective control. HAM-D has been selected as an outcome measure because of its frequent use in clinical studies of antidepressive

therapies (Rosenberg 2000), in order to provide directly comparable results. There are, however, many different ways to measure depression, of which HAM-D is not necessarily the most accurate (Rosenberg 2000).

Mean changes in DMN connectivity, activity, and TPN anti-correlation as well as depression severity will be compared between groups. It is expected that there will be a statistically significant decrease in mean Group B DMN activity. DMN connectivity is expected to decrease significantly, particularly within the anterior and posterior DMN, between the ACC and the anterior DMN, and between the ACC and the PCC. A significant decrease in mean HAM-D score is also anticipated. It is unclear how DMN-TPN anti-correlation will be altered in Group B, and how this will correlate with changes in HAM-D.

Within Group B, individual decreases in DMN activity and connectivity are expected to positively correlate with decreases in HAM-D score. Furthermore, individual decreases in DMN activity and connectivity are expected to positively correlate with intensity of subjective drug experience, suggesting that intensity of drug experience will also correlate with decrease in HAM-D score.

It is unclear how long changes in DMN activity and connectivity and in HAM-D score will last. It is likely that they will grow less significant over time, and may return to initial levels by the end of one year.

These results would provide evidence for the efficacy of psilocybin in treatment of MDD. More generally, such results would imply that DMN alteration could be used to treat psychopathologies. Future research should address the specific mechanisms by which psilocybin alters the DMN.

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