# Differences in personality, cognitive abilities, illicit drug use, and white matter structural integrity between hallucinogen users and matched controls

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# Abstract

Recent research has demonstrated potential therapeutic effects of hallucinogens, but little is known regarding enduring effects of hallucinogens on human brain structure. Preclinical findings suggest micro-scale structural neuroplastic changes after hallucinogen administration. The current study sought to investigate the association between hallucinogen use, macroscale brain structure, personality, cognitive ability, and illicit drug use in a naturalistic sample. Data from 53 subjects reporting ever having used hallucinogens and 53 approximately hallucinogen-naïve matched controls were drawn from the Nathan Kline Institute-Rockland Sample database. Participants had completed diffusion tensor imaging, psychological, behavioral, and psychiatric assessments. Groups were compared on measures of personality, cognitive ability, history of illicit drug use, and the density of white matter tracts determined from probabilistic tractography. Hallucinogen users reported greater lifetime use of illicit drugs than controls and scored higher on measures of openness to new experiences and cognitive ability. Hallucinogen users also had greater density of structural connectivity in white matter tracts that are thought to support cognition, emotion, and creativity. These findings are consistent with reports that hallucinogen use may lead to shifts in personality as well as multiple cognitive domains. These novel findings provide clues to potential neural mechanisms underlying therapeutic effects of hallucinogens.


# Introduction

The past decade has seen a resurgence of research on hallucinogen drugs, with studies investigating the safety and therapeutic efficacy[1–6] as well as psychological effects[6,7] of classic hallucinogens (e.g. serotonin 2A, or 5-$HT_{2A}$, receptor agonists). Recent studies have shown that only one or two doses of the classic hallucinogen psilocybin, administered within a psychotherapeutic context, lead to acute[8–10] and persisting[11,12] benefits in healthy volunteers, and persisting therapeutic benefit in patients with major depression disorder (MDD) [5,13], treatment-resistant depression[4,14], depression and anxiety associated with a late-stage cancer diagnosis[2,3], and tobacco[6,15] and alcohol use disorders[16]. Atypical hallucinogens such as dissociative anesthetics (NMDA antagonists like ketamine and dextromethorphan) have also demonstrated antidepressant effects[17–19], and 3,4-methylenedioxy-methamphetamine (MDMA) has shown great promise in the treatment of posttraumatic stress disorder[20–22].

Therapeutic use of classic hallucinogens has not yet made it into the clinic. Thus, information regarding controlled, purposeful use of these compounds for treatment purposes remains limited. Population-level surveys of naturalistic use have demonstrated that lifetime use of hallucinogens may confer some protection against suicidality and psychological distress[23,24]. However, hallucinogens can still confer psychological risk in uncontrolled settings. One survey reported on 1993 participants' most challenging psychological experience with recreational use of psylocibin [25]. Despite the majority of respondents indicating that the experience was among the top 10, 5, or single most challenging experience of their life, 84% felt they benefited from the experience, and 46% indicated that they would want to repeat the experience, including the challenging aspects. The median estimated dosage reported in this survey of

recreational use was 4g of dried mushroom, which is roughly equivalent to the 25mg (high) dose of psilocybin that is used as a therapeutic dose in laboratory settings[4,5,13]

Investigations of the psychological and neural mechanisms underlying therapeutic effects of hallucinogens are still in a nascent stage. While most studies of the acute effects of hallucinogens demonstrate impairments in a number of perceptual and cognitive domains[26–30], one recent study suggested a potential minute, acute attentional benefit of microdoses of LSD [31]. Another recent study demonstrated an improvement in cognitive flexibility in patients with MDD after treatment with psilocybin[32]. Enduring changes in personality, especially decreases in neuroticism[33–37] and increases in openness[38–40] as well as increases in mindfulness[39], have been reported after administration of classic hallucinogens. These cognitive and personality changes may be associated with psychological insights[5] and changes in psychological flexibility [7] that have been proposed to mediate enduring therapeutic effects of hallucinogens. However, studies of personality and cognition have primarily been conducted on moderately to highly selective samples rather than samples that are more generally representative.

Acute effects of classic hallucinogens on human brain function have been studied using many neuroimaging modalities. Radiological imaging techniques including single photon emission computed tomography (SPECT) and positron emission tomography (PET) have revealed hyperfrontality in regional cerebral blood flow (rCBF) during acute effects of mescaline[41] and ketamine[42,43] as well as increases of rate of cerebral glucose metabolism in the prefrontal cortex, anterior cingulate, temporomedial cortex, and putamen during acute effects of psilocybin[44]. Studies using functional magnetic resonance imaging (fMRI) have shown that classic hallucinogens acutely alter activity and connectivity of the thalamus[35,45–49], the default mode network[50–53], the claustrum[52] and task-positive brain networks, such as the fronto-parietal control network, and the salience network[54,55,52]. These and previous findings have supported models of acute psychedelic drug action that involve the disruption of cortical-subcortical circuits or canonical networks in the brain[56]. Atypical hallucinogens ketamine, dextromethorphan, and MDMA have been shown to alter connectivity within parts of the anterior cingulate[57–59], default mode network and salience network[57,59–64], though these compounds work through different molecular mechanisms (e.g. NMDA receptor blockade, or broad monoamine transporter reversal) than classic hallucinogens. Recent studies have suggested that both classic (N,N-dimethyltryptamine, LSD, psilocybin) and atypical (ketamine) hallucinogens have psychoplastogenic properties (e.g. neuritogenesis, spinogenesis, and synaptogenesis)[65–67]. Neural plasticity is attributed to TrkB, mTOR, and 5-$HT_{2A}$ receptor signaling, and might explain neurotherapeutic effects as well as structural changes observed in animal models of psychedelic drug effects on the brain.

Though there has been great progress in understanding the underlying neural mechanisms of acute hallucinogen effects, very few studies have examined enduring effects of psychedelic drugs on brain function[50,68–71], with only three studies to date investigating enduring effects of a psychedelic on brain function at a week or longer post-dose[32,72,73]. Most studies aim to investigate acute and near-term post-

acute effects (e.g. one or two days after hallucinogens administration), and to our knowledge no study has yet investigated the effects of a psychedelic on white matter structural connectivity. Changes in structural connectivity may occur at a longer time scale than acute subjective drug effects, or even measurements one or two days[68,69,71,74] or one week[32,72,73] after psychedelic experiences.

The current exploratory study investigated the association between lifetime hallucinogen use and brain structure, personality, illicit drug use and cognitive ability. Data from 106 subjects (53 of whom reported using hallucinogens in their lifetime) were drawn from a large community sample. Hallucinogen and non-hallucinogen-using groups were balanced for age, sex, and for current and prior psychiatric diagnoses. White matter structure was assessed using diffusion tensor imaging (DTI), and probabilistic tractography measures were compared between groups to test for associations between hallucinogen use and white matter density in a library of validated white matter tracts. A large battery of additional measures was also analyzed to test for group differences in personality, cognitive ability, and illicit drug use, and associations between white matter density and additional measures were tested. Based on current data in the literature, we hypothesized that hallucinogen users would exhibit greater openness, less neuroticism, and higher cognitive functioning scores, leaving open the expectation that groups would differ in density of white matter tracts that supporting these processes.

## Methods

# Participants and Data

Data were drawn from the Nathan Kline Institute-Rockland Sample[75], which is a publicly available dataset containing a wide array of physiological and psychological assessments, genetic information, and advanced neuroimaging outcomes in a lifespan sample (ages 6–85 years old). As part of a larger battery of measures, each participant completed measurements of drug use history, including the Comprehensive Addiction Severity Index for Adolescents (CASI-A) and the National Institute on Drug Abuse questionnaire (NIDA). Participants also completed psychiatric diagnostic questionnaires including Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) and Structured Clinical Interview for DSM-IV-TR Axis I Disorders – Non-Patient Edition (SCID-I/NP). All experiments were performed in accordance with relevant guidelines and regulations. Among 831 participants with Diffusion Tensor Imaging (DTI) data, 81 answered positively to the CASI-A question "Have you ever used a hallucinogen?" or the NIDA questionnaire item assessing lifetime hallucinogen use (the item specifies "LSD, acid, mushrooms, PCP, ketamine, ecstasy etc."). These participants were approximately matched in age and sex to 81 control participants who had consistently indicated in both the NIDA and the CASI-A questionnaires that they had NOT used a hallucinogen in their lifetime. A subset of individuals were then identified within this sample who were approximately matched for psychiatric diagnoses (including no psychiatric diagnosis) at the time of assessment, for a total of 53 hallucinogen users and 53 controls who were balanced on age, sex, and psychiatric diagnosis (see Supplementary Table 1 for a list of all NKI subject IDs included in the analysis).

# Analyses of Questionnaire and Psychiatric Assessment Data

Measures of personality, cognitive ability, and drug use history were compared between groups, given the potential enduring effects of hallucinogens on these domains [38, 76–82]. The NEO Five Factor Inventory (NEO-FFI-3) was used to assess the personality traits of Openness to Experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism[83]. Assessments of cognitive abilities included the Wechsler Abbreviated Scale of Intelligence (WASI-II) designed to assess specific and overall cognitive capabilities[84], the Wechsler Individual Achievement Test second edition abbreviated (WIAT-IIA)[85], and the Cognitive Failures Questionnaire (CFQ) assessing failures in perception, memory, and motor function in the completion of everyday tasks in the past 6 months[86]. Drug abuse questionnaires included the CASI-A and NIDA, assessing lifetime use of cannabis, cocaine, amphetamine-type stimulants, inhalants, sedatives, hallucinogens, opioids, alcohol, tobacco, and other miscellaneous drugs [87,88]. Unfortunately, too few respondents provided information regarding the frequency of use of most drugs of abuse, and thus a characterization of samples outside of lifetime use of these substances was not possible. Normality of the distributions of continuous data was assessed using Shapiro-Wilk test for normality. Two sample T-Tests were used for normally distributed data, and the nonparametric Mann Whitney U test was used for non-normally distributed data, to test for between-group differences in continuous outcome measures. Chi-square tests were used to assess group differences in categorical variables. Statistical analyses of questionnaire and psychiatric assessment data were performed using IBM SPSS statistics 22.0 software.

# DTI Acquisition, Preprocessing, and Analysis

DTI data were acquired in 137 directions, with 2mm isotropic voxel size, a b-value of 1500 s/mm², A > > P encoding direction, and multi-band acceleration factor of 4 using a Siemens Tim Trio 3T MRI. Image preprocessing and analysis was conducted using functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL). Steps included skull stripping using the brain extraction tool (BET)[89], followed by eddy current and motion correction[90] and DTIFIT for local fitting of diffusion tensors, resulting in a fractional anisotropy (FA) image for each subject. Voxelwise FA statistics were then generated using Tract-Based Spatial Statistics (TBSS). TBSS performs nonlinear registration of FA images to a standard space by projecting all subjects' FA data onto a mean FA skeleton[91]. A voxel-wise, two sample T-Test was then calculated to test whether FA differed between hallucinogen users and controls[92]. For statistical inference, including correction for multiple comparisons across space, maximal statistic permutation testing with threshold-free cluster enhancement (TFCE) was conducted[93] using RANDOMISE. The number of permutations to be performed was set at 5,000 for significant group differences at a level of $p < 0.05$ (FWE)[94].

# Tractography

Preliminary steps to tractography were performed by first using Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX). BEDPOSTX uses Markov Chain Monte Carlo sampling to build null distributions on diffusion parameters and models crossing fibers within each voxel of the brain[95]. Linear registration using FMRIB's Linear Image Registration (FLIRT) was applied. Diffusion space was registered to native structural space using high-resolution T1-weighted image of the same subject and then registered to standard space (MNI152 brain standard)[96–98]. Tractography was then performed on each subject using a cross-species tractography toolbox (XTRACT) with graphics processing unit (GPU) acceleration[99]. XTRACT performs probabilistic tractography using a library of validated tractography protocols for 42 white matter tracts (19 bilateral and 4 commissural in each hemisphere, see supplementary Table 2)[100]. Out of the 42 tracts, 2 tracts (Left and Right corticospinal tract) were removed due to insufficient number of subjects with full brain data coverage for these areas. Tract volume ($mm^3$) and the mean, median, and standard deviation of tract probability, length, fractional anisotropy, and mean diffusivity was extracted for each subject and for each of the 40 tracts that were analyzed [100]. A Shapiro-Wilk test for normal distribution demonstrated a non-normal distribution for tract-based statistics. Therefore, a nonparametric Mann-Whitney U test was used to assess group differences in summary statistics for each tract.

# White matter density comparison between groups

Separate voxel-wise general linear models (GLM) were estimated in FSL to compare white matter density between groups for each of 40 white matter tracts. GLM analyses for each tract were masked using the corresponding region of interest from XTRACT tract atlases generated from the human connectome project (HCP) data [100]. To control for potential effects of age, sex, and history of drug use on tractography-related outcome measures, statistical tests for Two-Group Difference Adjusted for Covariates were performed. All models were adjusted for age, sex, and previous drug use history of the subjects, and continuous variables were mean-centered. We then fitted a multiple covariates model to adjust for lifetime use of cocaine, stimulants, narcotics, and inhalants (as these were the drugs that showed significant differences between groups in lifetime prevalence of use). For statistical inference, including correction for multiple comparisons across space, maximal statistic permutation testing with TFCE was conducted using RANDOMISE. The number of permutations to be performed was set at 5,000 for significant group differences at a level of $p < 0.05$ (FWE)[94].

Association of white matter density with questionnaire assessments

Separate GLMs were estimated for each white matter tract that showed a significant difference in density between groups, to evaluate the association between differences in white matter density and differences in questionnaire assessment data between groups. Questionnaire scores that were significantly different between groups were included in the analysis. The regression also controlled for age, sex, and history of drug use. Continuous variables were mean-centered. For statistical inference, including correction for multiple comparisons across space, maximal statistic permutation testing with TFCE was conducted

using RANDOMISE. The number of permutations to be performed was set at 5,000 for significant group differences at a level of $p < 0.05$ (FWE)[94].

## Results

# Demographics

The demographic characteristics of both groups are detailed in Table 1. The majority of hallucinogen users and controls were females (60% and 58.5% respectively). Subjects represented a broad range of ages, from 17 to 77 years old. A small number of affective and other disorders were found in both control and hallucinogen users group s, but there were no significant differences between groups in the incidence of any diagnostic category (Table 2).

# Patterns of hallucinogen use

Age of first use of hallucinogens averaged 20.44 years (SD = 3.8 years, Fig. 1A). 71.15% of hallucinogen users reported never using hallucinogens on a “regular basis” (defined as at least once per month; Fig. 1B). 68.18% of hallucinogen users reported 0–1 years of regular use (Fig. 1C). No subjects used a hallucinogen in the month prior to their participation. 82% did not use hallucinogens in the year prior to their participation (Fig. 1D). In their peak pattern of use in the year prior to their participant, 15.91% (7 participants) of the 44 participant who answered this question used hallucinogens one to ten times and 2.27% (1 participant) used hallucinogens once per week, whereas the remainder indicated no hallucinogen use in the year prior to participation (Fig. 1E).

# Previous Use of Illicit Substances

CASI-A and NIDA questionnaire responses showed a significant difference between hallucinogen users and controls in the lifetime use of stimulants ($p = 0.023$), cocaine ($p = 0.000$), narcotics ($p = 0.004$), and inhalants ($p = 0.012$) in addition to hallucinogens ($p = 0.000$). There were no significant differences in use of tobacco ($p = 0.278$), marijuana ($p = 0.153$), alcohol ($p = 0.079$), and tranquilizers ($p = 0.22$) use (see Table 3).

# Personality Outcomes

Higher scores on the personality trait of openness to experience were observed in the hallucinogen users (M = 60, SD = 9) compared to controls (M = 56, SD = 9; $t = 2.321$, $p = 0.014$). No significant differences were observed in any other Big Five personality traits (see Supplementary Table 3).

# Cognitive Abilities

For scores on the WASI-II questionnaire, hallucinogen users (M = 61) had significantly higher total score (comprised from vocabulary, block design, similarities and matrix reasoning) than controls (M = 46; Mann-Whitney U = 1033, $p = 0.012$). A significant difference was found in verbal comprehension index scores in hallucinogens users (M = 61.1) compared to controls (M = 45.9; Mann-Whitney U = 1014.5, $p =$

0.008) as well as higher vocabulary (Mann-Whitney U = 981.5, p = 0.008) and similarities (Mann-Whitney U = 1079, p = 0.031) subset scores. Hallucinogen users also had significantly greater perceptual reasoning index scores (M = 60.25) compared to controls (M = 45.6; Mann-Whitney U = 1062.5, p = 0.024) as well as higher block design subset scores (M = 61.3) compared to controls (M = 45.7; Mann-Whitney U = 1014, p = 0.009). Hallucinogen users scored higher than controls on the following WIAT-IIA subscales: spelling (Mann-Whitney U = 1017, p = 0.021), numerical operations (Mann-Whitney U = 910, p = 0.009), and the composite standard score (Mann-Whitney U = 8897, p = 0.006). No significant group differences were observed in any of the Cognitive Failures Questionnaire (CFQ) scales, which assessed failures in perception, memory, and motor function in the completion of everyday tasks in the past 6 months found. Descriptive statistics for all cognitive assessment scores are presented in Supplementary Table 4.

# White matter integrity and structural connectivity

## Fractional Anisotropy-Based Measures

Significantly greater volume ($mm^3$) was observed in the hallucinogen users group (M = 57.98) than in controls (M = 46.135) (p = 0.044, Mann-Whitney-U = 1021) and larger mean tract probability was observed in the control group (M = 57.87) than in hallucinogen users group (M = 46.02; p = 0.044, Mann-Whitney-U = 1021) within the right inferior longitudinal fasciculus (ILF). Larger mean tract probability in the hallucinogen users group (M = 60.37) than in control group (M = 46.63; p = 0.021, Mann-Whitney-U = 1040.5) was also detected within the right superior thalamic radiation (STR). See supplementary table 5 for statistics for all tracts.

## Tractography-Based Measures

While our subjects are grouped by their history of hallucinogen use, there are also significant between-group differences in lifetime use of cocaine, stimulants, narcotics, and inhalants. Therefore, each of the 40 probabilistic white matter tract analyses was adjusted for the presence or absence of lifetime use of each of these four drugs, in addition to sex and age. After performing multi-covariate regression to correct for multiple drug use, we found greater density of white-matter tracts in the hallucinogen users group than in controls (Fig. 2A-F) in the left superior thalamic radiation (STR; p = 0.031), left arcuate fasciculus (AF; p = 0.026), left perigenual cingulum (CBP; p = 0.009), left (p < 0.001) and right (p = 0.035) frontal aslant (FA), right superior longitudinal fasciculus (SLF; p = 0.004), and left inferior longitudinal fasciculus (ILF; p = 0.017). Significantly less white matter tract density was observed in the hallucinogen users group compared to controls in the right inferior longitudinal fasciculus (ILF; p < 0.001) (Fig. 2G). A secondary analysis was performed after excluding two subjects who reported an atypical pattern of classic hallucinogen use ("once a month", "binge use", or peak use of "once a week") and their most closely matched controls (N = 4 removed). Six out of the 8 significant tracts remained significant: five tracts with greater density of structural connectivity in the hallucinogen users group, consisting of left STR (p = 0.018), left ILF (p < 0.001), left FA (p = 0.022), left AF (p = 0.008), right SLF (p < 0.001), and one tract with less density of structural connectivity in the hallucinogen users group, consisting of the right ILF (p =

0.003). Two tracts did not remain significant: left CBP and right FA. For the full list of the tracts and associated statistics, see Supplementary Table 2.

# Predictive analysis

WIAT-IIA word reading score was predictive of significantly greater density of structural connectivity in the left CBP ($p = 0.019$). WIAT-IIA domains of numerical score ($p = 0.024$), composite standard score ($p = 0.0009$), composite sum of subset standard scores including scores of word reading, numerical, and spelling subset scores ($p < 0.001$), and WASI-II vocabulary score ($p = 0.049$) were predictive of significant greater density structural connectivity in the left ILF. WASI-II domains of vocabulary ($p = 0.047$), verbal composite ($p = 0.037$) and full scale score ($p = 0.038$) were predictive of significant greater density structural connectivity in the right SLF.

## Discussion

The objective of this study was to determine if there was any association between lifetime hallucinogen use and personality, cognitive ability and brain structure in a natural sample of the population. Consistent with previous literature on the associations between hallucinogen use, personality, and cognition, significant differences were observed in trait openness and cognitive abilities between subjects who reported ever having used a hallucinogen and a control group that reported never having used hallucinogens. Hallucinogen users also reported greater lifetime use of illicit drugs. Finally, greater density of white matter tracts was observed in a number of white matter tracts implicated in the support of cognition, emotion, and creativity.

# Personality

Openness to experience is one of the major dimensions of the five-factor model of personality[101]. Individuals who score highly in openness are considered to be imaginative, sensitive to art and beauty, creative, and have a rich and complex emotional life[101]. They are intellectually curious[102], behaviorally flexible, and nondogmatic in their attitudes and values[103,101]. Individuals who score low in openness may be more likely to appreciate and rely on experiences and situations they have encountered before, since they are seen as safe.

Hallucinogen users in the current sample scored higher in personality trait of openness than controls. This is consistent with previous controlled laboratory experiments that demonstrated an increase in openness after classic hallucinogen administration. A moderate dose of LSD (75 µg intravenously) was shown to increase optimism and trait openness two weeks after administration[104]. In another study, openness increased in participants who had mystical experiences during their high-dose (30mg/70kg) psilocybin session, and remained significantly higher than baseline for more than one year after the session[105]. A recent PET study found limited association between 5-$HT_{2A}$ receptor availability and trait openness, warranting further study to evaluate 5-$HT_{2A}$ receptor-mediated mechanisms of change in

personality traits after intake of psilocybin[106]. Together, these findings suggest that psychedelic experience may increase openness. However, increased openness has also been shown to predict response to classic hallucinogens[107]. It is possible that those with higher openness scores to begin with are simply more likely to take hallucinogens than those with lower openness scores. Either way, our current findings are consisted with previously identified associations between greater openness and exposure to hallucinogens.

# Cognitive Ability

While administration of psychoactive doses of classic hallucinogens can acutely impair cognition [26–30,108,109], some evidence indicates either no effect or a modest cognitive benefit of classic hallucinogens at post-acute time points. Studies of ritual users of ayahuasca reported modest benefits in cognitive control in ayahuasca users[78,79]. A recent report also demonstrated an increase in cognitive control following psilocybin administration to patients with MDD[32]. Anecdotal reports on microdosing with psychedelic substances (psilocybin and LSD) suggest acute and post-acute cognitive enhancement (problem-solving and understanding), improved memory and clarity of thought[76], improved mood, cognition, and creativity[110], enhanced cognitive performance, and improved focus and productivity[111]. However, empirical evidence for such microdosing benefits is weak[31] to non-existent[112].

Hallucinogen users scored higher on measures of cognitive ability (e.g. WASI-II, WAIT-IIA) than controls. Specifically, on measures of word knowledge, verbal concept formation, crystallized intelligence, language development, abstract reasoning, associative and categorical thinking, and verbal expression. Hallucinogen users also scored higher on measures of analysis and synthesis of visual stimuli, nonverbal concept formation, fluid intelligence, visual perception and organization, and visual-motor coordination. Of course, in the current sample, causality of psychedelic use cannot be conclusively inferred. It may be that those who score higher on these tests are more likely to try hallucinogen drugs than those who score lower on these tests. However, these findings replicate previous findings of higher scores on cognitive tests in hallucinogen using groups compared to non-hallucinogen-using controls, and are consistent with a potential long-term cognitive benefit of psychedelic use, specifically in the domains of intelligence and cognitive flexibility.

# Previous use of illicit substances

The hallucinogen-using group in the current study reported greater lifetime use of illicit drugs than the control group. This is consistent with previous studies that have shown a progressive relationship between various forms of polydrug use. Though evidence is certainly mixed[113], the gateway theory suggest people who reported having used less common drugs were likely to have reported that they had also used more common drugs[114–116]. Administered in a clinical setting, however, psychedelic drugs may help to reduce or eliminate problematic substance use[6,77]. Naturalistic, recreational psychedelic use in some cases may also lead to reduction or elimination of illicit substance use[80,82,117] in addition to other

psychological benefits[23,117–122], though the rate of this occurrence is not clear. Recent anonymous survey studies found 343 individuals who reported reducing or stopping alcohol use[81], 358 individuals who reported reducing or quitting smoking[82], and 444 individuals who reported reductions in cannabis, opioid, and stimulant misuse[80], after taking a psychedelic drug in a non-clinical setting. Most of the respondents in these surveys reported lasting reductions in their substance use over 1 year after using a hallucinogen, findings consistent with persisting benefits observed in controlled studies with psilocybin and smoking cessation[15] and alcohol dependence[16].

In the current study, lifetime use of cannabis, tobacco, alcohol, and tranquilizers was not significantly different between groups, but cocaine, stimulant (other than cocaine), narcotic, and inhalant use was significantly higher in the hallucinogen users group. However, it is unclear whether this illicit drug use preceded, followed after, or was concurrent with hallucinogen use. Although comprehensive information regarding the extent of illicit drug use is not available in the current sample, 7.4% of subjects in the hallucinogen user group and 5.6% of subjects in the control group reported a current diagnosis of substance use disorder related to alcohol or cannabis at the time of the assessments. Since groups were cross-sectional and roughly matched for psychiatric diagnoses, this precludes any finding regarding the effects of hallucinogen use on substance use disorder diagnosis, prevalence, duration, or severity (or the prevalence or severity of other psychiatric disorders, such as mood disorders).

# White Matter Structure

Classic hallucinogens (5-$HT_{2A}$ receptor agonists) such as lysergic acid diethylamide (LSD), psilocybin, and N,N-dimethyltryptamine (DMT) and dissociative hallucinogens (NMDA receptor antagonists) such as dextromethorphan (DXM) and ketamine may share neuropsychological[26] as well as neuropsychoplastogenic[123] effects despite their different pharmacology. Previous studies described short term effect of various hallucinogens on brain network activity and connectivity[41,43,50,71,72,124], however, to our knowledge, no previous study has investigated long-term changes in white matter structure after hallucinogen use. The current study reports greater density of structural connectivity among hallucinogen users when analyzing seeds and tracts for the left superior thalamic radiation, left perigenual cingulum, left arcuate fasciculus, left and right frontal aslant, right superior longitudinal fasciculus and the left inferior longitudinal fasciculus. Lower density of structural connectivity was observed in the hallucinogen users group in the right inferior longitudinal fasciculus.

The *inferior longitudinal fasciculus* (ILF) is a long-range white matter pathway that supports the ventral visual stream (the “what” pathway, as opposed to the “where” pathway), connecting the occipital and temporal-occipital areas of the brain to anterior temporal areas[125,126] in support of object recognition processes. Thus, this pathway plays a major role in a large array of perceptual and cognitive functions[125]. The ILF demonstrates a strong leftward-lateralized connectivity pattern that suggests an additional role in the semantic system[127]. The left ILF was also shown to have a critical role in reading-related visual information processing[125], with fractional anisotropy of the ILF correlating with reading

comprehension[128–131] and lexical/semantic task performance[131–134]. Thus, the current findings of greater structural connectivity in the left ILF are consistent with higher perceptual reasoning scores in the current hallucinogen users group, and better performance on verbal memory tests in previous studies of hallucinogen users[135]. This is further supported by positive associations between WIAT-IIA and WASI-II scores and density of structural connectivity of the left ILF.

Previous DTI studies demonstrated a double dissociation between the functions of the right ILF and those of the fornix with respect to visual processing; white matter integrity in the ILF (though not in the fornix) was strongly associated with face processing performance, while white matter integrity in the fornix (though not in the ILF) were found to be associated with scene processing performance[125,136]. Studies comparing healthy individuals and patients with brain damage suggest that a functional right ILF is crucial for efficient face recognition[125,136,137]. The ILF serves as a structural pathway between the amygdala and visual cortex, and is also involved in the integration of visual and emotional processes[125].

Lower mean tract probability and density of structural connectivity in the right ILF in hallucinogen users compared to controls in the current sample is therefore quite intriguing in the context of other recent findings. Acute[9,10] and persisting[52,68] reductions in amygdala response to negative facial emotional expressions have been demonstrated, and may be associated with an enduring reduction in negative affect and antidepressant, anti-anxiety, and pro-positive-affective responses to psychedelic drug administration. It may be that observed, persisting reductions in amygdala reactivity and negative affect are a function of reduced white matter density or integrity in the right ILF.

*The Superior Thalamic Radiation (STR)* connects the ventral nuclear group of the thalamus with the precentral and the somatosensory area of the postcentral gyrus through the superior thalamic peduncle and the posterior limb of the internal capsule[138,139]. This is a pathway that involves a number of brain regions that are engaged during psychedelic drug effects. Specifically, the cortico-striato–thalamo-cortical (CSTC) gating hypothesis of psychedelic drug action[140] proposes that psychedelic drug effects may result from disruption of thalamo-cortical and striatal-thalamic pathways involved in sensory processing[56]. Greater global connectivity of thalamic and sensory-somatomotor regions has been observed during acute effects of both LSD[35] and psilocybin[141], and LSD has been shown to alter effective thalamo-cortical thalamo-striatal connectivity[46], consistent with psychedelic disruption of sensory and sensorimotor processes. The current finding of greater mean tract probability and density of structural connectivity in the left STR is consistent with a crucial role of the thalamus in hallucinogen effects, and consistent with hallucinogen exposure leading to long-term alteration of circuits that are altered acutely, though the functional significance of altered thalamic structural connectivity in this context is not precisely clear.

The *cingulum* bundle is a distinctive fiber tract in the brain, forming a near-complete ring from the orbital frontal cortices, along the dorsal surface of the corpus callosum, then down through the temporal lobe towards the temporal pole[142]. Clinical studies reveal cingulum abnormalities in various conditions,

including schizophrenia, depression, posttraumatic stress disorder, obsessive compulsive disorder, autism spectrum disorder, mild cognitive impairment, and Alzheimer's disease[142]. Imaging studies have implicated disruptions in the anterior cingulum in the pathophysiology of mood disorders[143,144] and have found associations between lower structural integrity of white matter tracts of the left anterior cingulum and presence of unipolar depression or bipolar disorder[143–145]. As such, the anterior cingulum became a target for numerous treatments for depression including deep brain stimulation[144], ECT[143], and even anterior cingulotomy for refractory depression[146,147], refractory obsessive compulsive disorder[148,149] and chronic pain[150,151]. Imaging studies also found association between structural integrity of white matter tracts of the left anterior cingulum and wide range of cognitive functions, including attention, executive functions, memory performance, fluency, verbal and symbolic tasks performance[142,152]. When examining density of structural connectivity in the perigenual cingulum, the current analysis yielded greater density of structural connectivity in the hallucinogen users group. This suggests that a possible neurobiological mechanism underlying the therapeutic effects of hallucinogens in the treatment of depression[3–5] and reduced risk of suicidality[23,24,118,153] may be partly related to hallucinogen-evoked changes in the anterior cingulum. This finding is also consistent with previous findings of higher scores on cognitive function tasks in hallucinogen using groups.

The *frontal aslant* (FA) is a white matter pathway that connects the inferior frontal gyrus with the supplementary motor area (SMA) and the pre-SMA [154,155]. The FA plays an important role in motor control during speech production[155]. Imaging studies have shown that the left FA may play a role in speech initiation, verbal fluency, and stuttering[155,156]. Integrity of the right FA may be associated with certain executive functions, and specifically inhibitory control[156,157]. The current study found greater density structural connectivity in the hallucinogen using group in both left and right FA. These findings are generally consistent with overall higher performance on tests of cognitive abilities in hallucinogen using groups in the current study as well as previous studies, though the precise functional significance of altered bilateral FA structural connectivity in this context is not precisely clear.

The *arcuate fasciculus* (AF) is a white matter pathway that connects temporal, frontal and parietal cortices[158,159]. This tract plays a critical role in several cognitive functions related to phonological and language processing [159,160]. Imaging studies have found associations between lesions in the left arcuate fasciculus and impairment in speech production[161], aphasia[162] and depressive symptoms in patients with multiple sclerosis[163]. Greater AF white matter density observed in the hallucinogen users in the current study is consistent with higher verbal comprehension scores in hallucinogens users in the current dataset and higher performance in lexically-focused tasks in previous studies[78,79].

The *right superior longitudinal fasciculus* (SLF) is a long white matter pathway that extends from the anterior region of the cortex (e.g. prefrontal cortex) to the posterior region (e.g. parietal cortex) [164]. Greater integrity of the right SLF is associated with better performance in non-verbal auditory[165], attention[164,165], and visual-spatial tasks[164,166]. White matter integrity in the SLF was also found to correlate positively

with openness[167,168]. Findings of greater white matter density in the right SLF in the hallucinogen users group are consistent with higher perceptual reasoning scores demonstrated in the hallucinogen users group compared to the control group.

*Overall*, the current findings provide evidence for a potential white matter structural consequence of exposure to hallucinogens. White matter density is generally greater in hallucinogen users, compared to controls, in canonical tracts that are associated with perception, cognition, and affect. If we can generally assume that greater white matter density within a tract confers a processing benefit, and that lower white matter density could represent a processing deficit, the current findings are consistent with previous findings suggesting improved cognitive function and reduced negative affect among hallucinogen users. Though it is not possible from the present data to conclusively ascribe causal functional significance to between-group differences in white matter structure, it is notable that differences in white matter density in the current sample are localized to regions that are associated with functional alterations reported during the acute effects of hallucinogens. Given proposed psychoplastogenic effects of hallucinogens[67,169], it may be that circuits or pathways that are acutely altered during hallucinogen drug action are open to undergoing some lasting structural change that can be observed with diffusion imaging methods.

# Limitations

Subjects were drawn from NKI-RS database of natural general population sample. Subjects were selected according to their report of ever (or never) having used hallucinogens. Since the study population reflected a natural sample, some of the subjects had psychiatric diagnoses and previous drug use. We attempted to mitigate these effects by balancing the groups in criteria of age, sex, and psychiatric diagnoses, and this led to groups that were also balanced for previous use of alcohol, tobacco, and cannabis, as well as scores on measures of depression, anxiety and trauma. Given the cross-sectional nature of this dataset, we cannot conclusively determine whether hallucinogen users scored higher due to their use of hallucinogens, or whether individuals with higher cognitive scores and openness to new experiences are more likely to use hallucinogens. Given that we explicitly matched groups on psychiatric diagnosis, and the majority of individuals in both groups did not have a diagnosis, we are unable to make any statements regarding the effects of lifetime use of a hallucinogen on psychopathology (though others have done so[118,170]). However, our findings are consistent with previous studies suggesting that hallucinogens may confer cognitive benefit[32,78,79,135,171] and increase openness[21, 38–40,105,172,173]. While we were interested in directly assessing the association between personality and cognitive ability scores and white matter integrity, some of these relationships were difficult to interpret. The observed relationship between word reading scores and differences in CBP white matter density and WASI-II scores and right SLF white matter density escape immediate interpretation. Replication of these findings in a longitudinal study and more direct assessment of cognitive abilities with carefully-controlled behavioral tasks in a prospectively sampled and controlled study population may address some of these limitations.

# Conclusions

The current report compared a group of individuals who have used hallucinogens in their lifetime to a control sample who report never having used hallucinogens. Individuals who used hallucinogens performed better on a wide array of cognitive ability assessments that are broadly associated with intelligence, consistent with previous findings in the literature suggesting cognitive benefit conferred to regular users of peyote [171] and ayahuasca[79]. Hallucinogen users also scored higher on the personality trait of openness to new experiences, which is believed to reflect higher creativity, intellectual curiosity, and cognitive flexibility. This is consistent with previous findings of increased openness after controlled hallucinogen administration[38,105,172]. Differences were observed in the density of white matter tracts that may support findings of higher cognitive performance and increased openness, providing a potential neural mechanism underlying persisting psychological benefits that have been described in both healthy and clinical populations.

# Declarations

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**Author Contributions**: Dr. Aharon-Almagor prepared data, designed and conducted all analyses, and wrote the first draft of the manuscript. Dr. Barrett conceived of the project and provided supervision and guidance for data preparation and analysis. Both authors edited the manuscript and prepared the figures.

### Availability of Data and Materials

The datasets generated and analyzed during the current study are available in the Nathan Kline Institute-Rockland Sample[75] MRI database repository, [COINS: Collaborative Informatics and Neuroimaging Suite (trendscenter.org)]. View supplementary table 1 for the NKI database IDs.

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# Tables

**Table 1** Demographics

| Variables | Hallucinogen users (N=53) | Control (N=53) | P-value | Chi-square value (df*, N) | Mann-Whitney U |
|---|---|---|---|---|---|
| Sex (%) | | | 0.842 | 0.04 (1,106) | |
| male | 21 (40%) | 22 (41.5%) | | | |
| female | 32 (60%) | 31 (58.5%) | | | |
| Age Mean (SD) | 43.13 (15.14) | 43.24 (15.79) | 0.940 | | 1392.500 |
| | | | | | |
| *df-degree of freedom | | | | | |

**Table 2** Current diagnoses

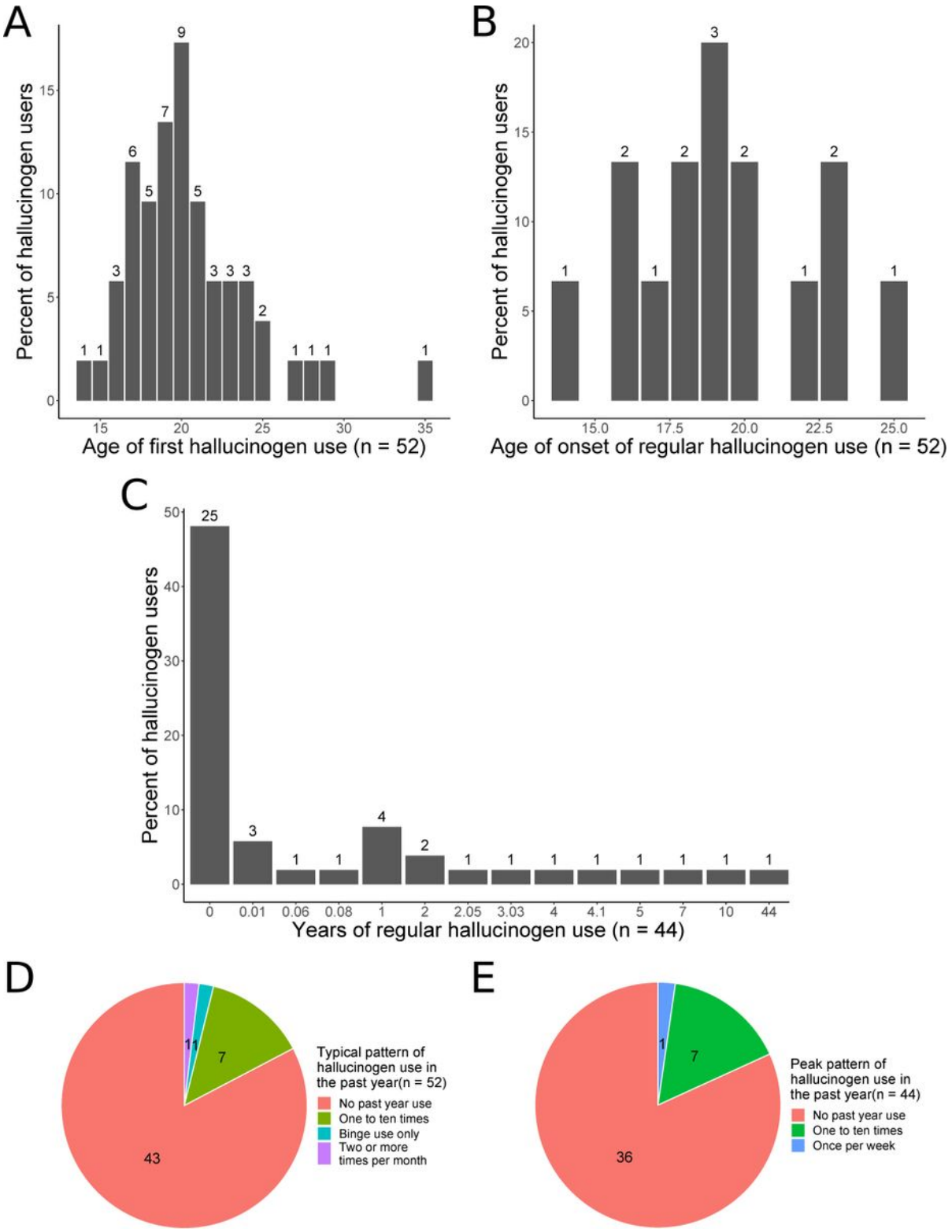
| Current diagnoses | Group | | P-value | Pearson Chi-Square |
|---|---|---|---|---|
| | Hallucinogen users (N=53) | Controls (N=53) | | |
| No Diagnosis or Condition on Axis I | 39 (74%) | 39 (74%) | 0.948 | 3.991 |
| Major Affective disorders | 2 (3.7%) | 1 (1.8%) | | |
| Dysthymic disorder | 2 (3.7%) | 2 (3.7%) | | |
| ADHD | 3 (5.6%) | 3 (5.6%) | | |
| Alcohol abuse | 1 (1.8%) | 0 (0%) | | |
| Cannabis abuse | 3 (5.6%) | 3 (5.6%) | | |
| specific phobia | 1 (1.8%) | 2 (3.7%) | | |
| Panic disorder | 1 (1.8%) | 3 (5.6%) | | |
| GAD | 1 (1.8%) | 2 (3.7%) | | |
| OCD | 1 (1.8%) | 1 (1.8%) | | |
| PTSD | 2 (3.7%) | 1 (1.8%) | | |
| Eating disorder | 1 (1.8%) | 0 (0%) | | |

**Table 3** Past drug use

| Past use of Hallucinogens | | | | |
|---|---|---|---|---|
| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
| Yes | 53, 100% | 0, 0% | 106.000, | 0.000 |
| No | 0, 0% | 53, 100% | | |
| Past use of Tobacco | | | | |
| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
| Yes | 47, 88.7% | 43, 81.1% | 1.178 | 0.278 |
| No | 6, 11.3% | 10, 18.9% | | |
| Past use of Marijuana | | | | |
| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
| Yes | 53, 100% | 51, 96.2% | 2.038 | 0.153 |
| No | 0, 0% | 2, 3.8% | | |
| Past use of Stimulants (other than cocaine) | | | | |
| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
| Yes | 14, 26.4% | 5, 9.4% | 5.194 | 0.023 |
| No | 39, 73.7% | 48, 90.6% | | |
| Past use of Cocaine | | | | |
| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
| Yes | 32, 60.4% | 14, 26.4% | 12.719 | 0.000 |
| No | 21,39.6% | 39, 73.6% | | |
| Past use of Narcotics | | | | |
| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
| Yes | 14, 26.4% | 3, 5.7% | 8.477 | 0.004 |
| No | 39, 73.7% | 50, 94.3% | | |
| Past use of Inhalants | | | | |
| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
| Yes | 6, 11.3% | 0, 0% | 6.360 | 0.012 |
| No | 47, 88.7% | 53, 100% | | |
| Past use of Alcohol | | | | |

| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
|---|---|---|---|---|
| Yes | 53, 100% | 50, 94.3% | 3.087 | 0.079 |
| No | 0, 0% | 3, 5.7% | | |
| Past use of Tranquilizers | | | | |
| | Hallucinogen users (N, %) | Controls (N=53) | Pearson Chi-Square | P-value |
| Yes | 8, 15.1% | 4, 7.5% | 1.504 | 0.220 |
| No | 45, 84.9% | 49, 52.1% | | |

# Figures




## Figure 1

Characteristics of hallucinogen use in the hallucinogen users group. Bar graphs plot the distribution of (A) the age of first hallucinogen use, (B) the age of onset of regular hallucinogen, and (C) the length, in years, of regular hallucinogen use for those who responded to each question. Percentage, out of all of hallucinogen users who answered a given question, is plotted on the Y-axis, the count of hallucinogen users at each point in the distribution is plotted at the top of each bar, and the number of subjects who

answered each question is presented in the title for the X-axis. Pie charts depict (D) the typical pattern of hallucinogen use in the year prior to completing the study, and (E) the peak pattern of hallucinogen use in the year prior to completing the study, with the number of subjects who answered each question presented in the legend title for each pie chart.

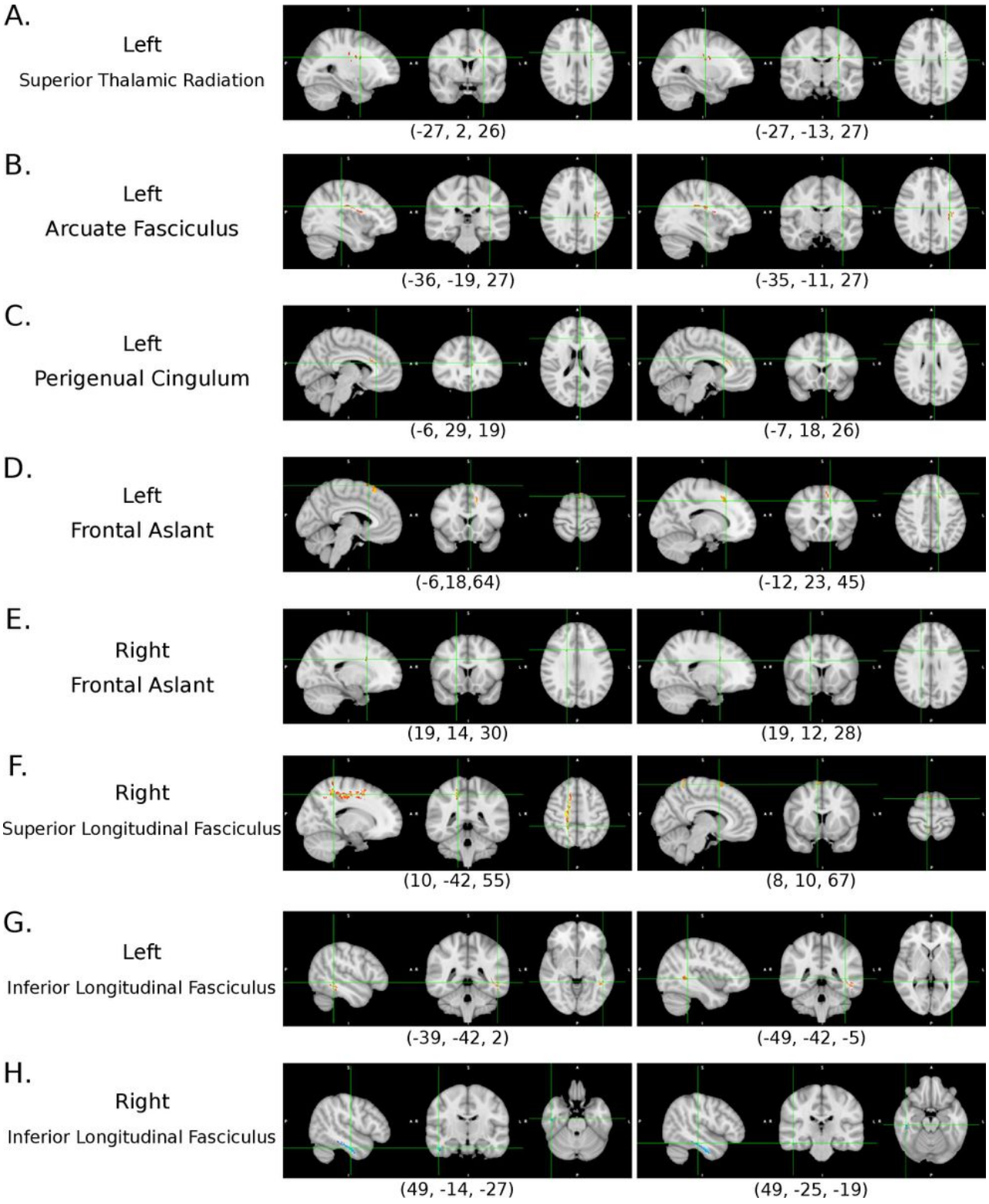



**Figure 2**

Between-group differences in the density of white matter tracts. Sagittal, coronal, and axial slices are presented in radiological convention for each of eight white matter tracts that show significant differences between hallucinogen users and controls. MNI coordinates for each triplicate of slices are present below each triplicate. Red voxels indicate areas of greater density of white matter tracts in hallucinogen users than in controls. Blue voxels indicate areas of greater density of white matter tracts in controls than in hallucinogen users. Images are thresholded to correct for family-wise error rate ($p < 0.05$).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytables14.docx
- supplementarytable5.xlsx