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Common gray matter loss in the frontal cortex in patients with methamphetamine-associated psychosis and schizophrenia

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ABSTRACT

Background and hypothesis: Methamphetamine (MA)-associated psychosis has become a public concern. However, its mechanism is not clear. Investigating similarities and differences between MA-associated psychosis and schizophrenia in brain alterations would be informative for neuropathology.

Study design: This study compared gray matter volumes of the brain across four participant groups: healthy controls (HC, n = 53), MA users without psychosis (MA, n = 22), patients with MA-associated psychosis (MAP, n = 34) and patients with schizophrenia (SCZ, n = 33). Clinical predictors of brain alterations, as well as association of brain alterations with psychotic symptoms and attention impairment were further investigated.

Study results: Compared with the HC, the MAP and the SCZ showed similar gray matter reductions in the frontal cortex, particularly in prefrontal areas. Moreover, a stepwise extension of gray matter reductions was exhibited across the MA – MAP – SCZ. Duration of abstinence was associated with regional volumetric recovery in the MAP, while this amendment in brain morphometry was not accompanied with symptom's remission. Illness duration of psychosis was among the predictive factors of regional gray matter reductions in both psychotic groups. Volume reductions were found to be associated with attention impairment in the SCZ, while this association was reversed in the MAP in frontal cortex.

Conclusions: This study suggested MA-associated psychosis and schizophrenia had common neuropathology in cognitive-related frontal cortices. A continuum of neuropathology between MA use and schizophrenia was tentatively implicated. Illness progressions and glial repairments could both play roles in neuropathological changes in MA-associated psychosis.

1. Introduction

Methamphetamine (MA) abuse constitutes a serious global public health issue. MA-associated psychosis is a psychotic disorder caused by MA use. MA users have been reported to be 11 times more likely to develop psychosis than general population (Voce et al., 2019; Arunogiri et al., 2018). About 10 % to 64 % of MA users suffered from the drug associated psychosis (Glasner-Edwards and Mooney, 2014); (Hsieh et al., 2014). Similar to those of schizophrenia, the symptoms of MAP include hallucinations and delusions, with auditory hallucinations, persecutory and reference delusions presented most frequently (Yang et al., 2020). The course of the disorder varies across users. Some patients experience acute and transient psychotic syndrome, whereas others maintain symptoms even after MA use has been discontinued for many months or years, or they experience recurring episode of the syndrome without the drug use (Glasner-Edwards and Mooney, 2014; Chiang et al., 2019). Patients with MA-associated psychosis are involved in violence, crime and suicide, and suffered from poorer prognoses than those MA users without psychosis (Glasner-Edwards and Mooney, 2014; Darke et al., 2019; McKetin et al., 2014; Grant et al., 2012); while mechanisms underlying this condition are not clear yet (Chen et al., 2019).

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MA-associated psychosis resembles schizophrenia in clinical symptoms, and has been proposed as a pharmacological model of schizophrenia in animal studies (Winship et al., 2019; Oka et al., 2020). Antipsychotics for schizophrenia had also been evidenced to be efficacious in treatment of severe symptoms of psychotic disorders induced by MA use (Fluyau et al., 2019). However, connections of the two disorders in neuropathology of clinical subjects have seldom been investigated.

Several neuroimaging studies have shown brain deficits in patients with MA-associated psychosis (Aoki et al., 2013; Uhlmann et al., 2016; Uhlmann et al., 2016; Yang et al., 2021; Ipser et al., 2018), including volumetric/thickness reductions in the frontal or temporal gray matter (Aoki et al., 2013; Uhlmann et al., 2016), regional homogeneity (ReHo) alterations in resting-state brain activity (Yang et al., 2021), connectivity dysregulation within intrinsic brain networks (Ipser et al., 2018), as well as widespread impairment in the white matter integrity. And some of the brain deficits have been reported to be specific to patients with MA-associated psychosis in contrast to those MA patients without psychosis (Uhlmann et al., 2016; Uhlmann et al., 2016; Ipser et al., 2018; Fassbender et al., 2015). For example, Uhlmann et al. (Uhlmann et al., 2016) demonstrated in their study that the impairment in white matter integrity was shown in MA use participants with associated psychosis, while not in non-psychotic MA use participants relative to control participants. Furthermore, some previous studies have indicated that brain regions affected in patients with MA-associated psychosis could be also involved in the brain abnormalities of schizophrenia (Aoki et al., 2013; Uhlmann et al., 2016). However, far less study up-to-date have compared MA-associated psychosis with schizophrenia directly among clinical subjects in brain alterations. In addition, researches currently available in this direction have yield inconstant findings.

Previously, applying task-based near-infrared spectroscopy, Yamamuro et al reported patients with MA-associated psychosis and those with schizophrenia were differential in prefrontal activities when performing verbal fluency tasks. While Okada et al. demonstrated that MA-associated psychosis and schizophrenia participants were similar in activation reductions in bilateral ventrolateral prefrontal cortex, while they were differential activated in the frontopolar, with participants suffered MA-associated psychosis showing less actived in this specific area when performing a stop-signal inhibitory task (Okada et al., 2016). Of more recent studies using magnetic resonance imaging (MRI) techniques, Zhang and colleagues (Mancuso et al., 2020) demonstrated that patients with MA-associated psychosis and schizophrenia showed different changes in regional gray matter density, regional homogeneity and seed-based functional connectivity in the brain's resting-state. In contrast, one of our previous studies showed that MA-associated psychosis and schizophrenia had a same direction of ReHo alterations in the brain, both in bivariate frontal-temporal cortex and left putamen (Yang et al., 2021). Inconsistency relating to results and methodologies between studies prevent conclusive evidence to illustrate connections as well as differences in neuropathology between the two psychotic conditions. Furthermore, to the best of our knowledge, none of available studies had compared brain alterations in MA-associated psychosis parallelly with both schizophrenia and non-psychotic MA users.

Structural magnetic resonance imaging (MRI) can present volumetric changes of the brain in clinical subjects and had been applied to multiple neuropsychiatric disorders (Mancuso et al., 2020; Pando-Naude et al., 2021). With structural MRI, voxel-based morphometry (VBM) approach provides the voxel-wise estimation of local amount or volume of a specific tissue compartment, and is most often applied to investigate local distributions of gray matter (Christian, 2020). In this current study, structural MRI with VBM approach was used to investigate and compare brain alterations in gray matter across patients with MA-associated psychosis, patients with schizophrenia and those MA users without psychosis. In addition, clinical factors associated with brain alterations, as well as the association of gray matter changes with psychometric variables, particularly with respect to psychotic symptoms and impaired attention vigilance in psychotic patients (Nuechterlein et al., 2015; Klein et al., 2020), were further investigated.

Based on current literatures and the dopaminergic hypothesis in schizophrenia (Chen et al., 2019; Mubarik and Tohid, 2016); and given the acute dopaminergic effects of MA use (Jan et al., 2012), we hypothesized that both MA-associated psychosis and schizophrenia have similar gray matter alterations compared to healthy individuals, particularly in brain regions involved in the mesocortico-limbic pathway. We also expected an association of MA use indices with brain alterations in MA-associated psychosis.

2. Methods

2.1. Participants

All participants were recruited from Shenzhen Kangning Hospital and local communities, with online and poster advertisements, or by invitation with mouth. Participants were enrolled into four groups: patients with MA-associated psychosis (MAP, n = 34), patients with schizophrenia (SCZ, n = 34), MA users without psychosis (MA) (n = 22), and healthy controls (HC) (n = 54). The participants were required to have normal or corrected-to-normal vision, normal hearing, aged from 18 to 59, and belongs to Chinese Han in ethnicity. Clinical diagnoses were assessed applying the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 2002). The SCZ met the DSM-IV diagnostic criteria (First et al., 2002) after hospitalized treatment for their first episode of the disorder. The MAP met a lifetime diagnosis of MA-induced psychosis, while the course of symptoms could be longer than 6 months. The MA received a diagnosis of MA dependence or abuse, without current or past psychotic symptoms. Participants in the HC were also assessed with SCID-I for being free of any DSM-IV axis I diagnosis.

Subjects were excluded if they had any severe neurological disease, head trauma, cardiovascular disease and physical illness. Those with other psychiatric disorders in the DSM-IV axis I, or abuse of other substances, except for tobacco, coffee, and alcohol drinking without alcoholism, were also excluded. Females in pregnancy, and participants who were incompatible with MRI (claustrophobia, metal objects in body, etc.) were further excluded. All participants received physical examinations, routine blood tests, AIDS/HIV screening and electrocardiographic check. Urine toxicology screens for amphetamine, methamphetamine, cocaine, morphine and cannabis were conducted for each participant to confirm his/her drug use report.

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 (World Medical Association. Declaration of Helsinki, 2008). All procedures involving human subjects were approved by approved by the Research Ethics Committee of Shenzhen Kanging Hospital (2019-k003-01). All the participants had provided written informed consent after receiving a full explanation of the study.

2.2. Clinical assessment

A research assistant conducted initial contacts with potential participants. The formal study interview and the MRI scan were arranged on a consultative basis. Clinical assessment and SCID-I were administered by a trained attending psychiatrist (Kong Z, one of the co-authors) in the study interview during 24 h before the MRI scan. After general (demographic and clinical) information collection and the SCID-I (Swanson et al., 2011) assessment for DSM-IV diagnoses, patient groups were evaluated for psychotic symptoms using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). MA use patients (including the MA and the MAP) also completed a timeline follow back of the UCLA Natural History Interview (NHI) to collect drug use information in detail; and their current drug use severity were furtherly assessed with drug use subscale of the Addiction Severity Index (ASI-drug). When available, medical records were consulted and family members were

interviewed to aid in the assessment for patients. After completion of the study, 200 Chinese yuan was paid to each participant in appreciation to his/her time consumption.

2.3. Attention vigilance measurement

Cogstate card-based identification test was administered to assess participant's attention vigilance, on a personal desktop computer. The test was performed among the Cogstate Schizophrenia Battery (CSB). Cogstate is a commercial based digital cognitive testing system, returning measure outcomes online (https://www.cogstate.com/). The CSB has been validated under diverse cultures as well as in multiple countries, including China (Zhong and Zhao, 2019). Accuracy (ACC, arcsine transformation of the square root of the proportion of correct responses) and speed (LMN, mean of the log10 transformed reaction times for correct responses) of the test performance were select as the outcome measures.

2.4. MRI acquisition

MRI data were acquired on a 3.0 Tesla Magnetic Resonance (MR) system (Discovery MR750 System, GE Healthcare) with an eight-channel phased-array head coil. The subject's head was cushioned with attached earmuffs. The 3D high-resolution structural images were acquired using a T1-weighted fast spoiled gradient echo (SPGE) sequence. The following parameters were used: TR = 6.7 msec, TE = 2.9 msec, TI = 450 msec, Flip Angle (deg) = 12°, FOV = 256 × 256 mm (Arunogiri et al., 2018), matrix = 256 × 256, slice thickness = 1 mm, gap = 0 mm, NEX = 1, iPAT/Aset = 2, Voxel size = 1 × 1 × 1 mm, Orientation = Sagittal, Bandwidth = 31.25 kHz, Slice Num. = 176.

2.5. Image preprocessing

Image data were preprocessed and analyzed using the CAT12 (Christian Gaser and Robert Dahnke, Jena University Hospital, Jena, Germany; https://dbm.neuro.uni-jena.de/cat/), an extension to SPM12 (Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK; https://www.fil.ion.ucl.ac. uk/spm/software/spm12/). For preprocessing, pre-set parameters in accordance with standard protocol of VBM in the CAT12 (https://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) were employed, used as default settings unless indicated otherwise. Data quality was controlled with three-steps: first, all images were visually inspected for artifacts (prior to pre-processing); second, between-subject homogeneity of the modulated normalized gray matter segments derived from the pre-processing was checked for each participant group (with "check sample homogeneity" module), and outliers were carefully inspected for artifacts or pre-processing errors. Lastly, after the pre-processing, a visual inspection was again conducted for each subject's gray matter image (with "display-one slice for all images" module), to check whether the process yielded reasonable results, excluding any newly introduced artifacts, and adjusting any biased orientations of the images. After the quality controls, two participants (1 HC and 1 SCZ) were excluded, yielding a sample of 142 for statistical analysis (53 HC, 22 MA, 34 MAP and 33 SCZ). Finally, the modulated normalized gray matter images were smoothed with an 8 mm FWHM Gaussian kernel before entering statistical analysis. Moreover, the total intracranial volume (TIV) for each scan was estimated (with "get TIV" module") to serve as an adjusting covariate for volumetric variances.

2.6 vol. -based morphometry analysis

Differences in gray matter volumes of the brain were examined with one-way ANOVA across the four participant groups (i.e., HC, MA, MAP and SCZ), followed by a set of *post-hoc* two-sample t-tests. The ANOVA was conducted in whole-brain, and the following post-hoc tests were conducted within the subset of clusters as a whole showing significant main effect in the ANOVA. To avoid possible edge effects between different tissue types, all voxels with gray matter value < 0.2 were excluded (absolute threshold masking). All comparisons were conducted while controlling for the variables of sex, age, education, smoking and drinking, as well as TIV. Threshold-free cluster enhancement (TFCE) with 5000 permutations and family-wise error (FWE) correction was conducted to control false positive results. Any clusters with voxel-wise TFCE-FWE corrected $p < 0.05$ was consider to be significant. The automated anatomical labeling atlas 3 (AAL3) was used to label brain regions.

For following association and comparison studies, mean volume value (averaged voxel strength) of each cluster derived from above VBM analyses were extracted out for each participant with ROI Signal Extractor in DPABI (https://rfmri.org/DPABI) (AAPP et al., 2022).

In addition, a set of subgroup comparisons in gray matter volumes with VBM among the MAP (subjects ever received antipsychotic treatment vs subjects ever not; subjects taking antipsychotics currently vs subjects currently not; subjects with current psychotic symptoms (defined in this study as PANSS-positive score ≥ 13 with at least two items for positive symptoms ≥ 3) vs subjects without (PANSS-positive scale score ≤ 9), respectively) was performed to account for effects of antipsychotics treatment on gray matter volumes, and to examine if volumes associated to current psychotic symptoms presented in the MAP. For these subgroup comparisons, t-tests with controlling for sex, age, education, smoking and drinking, as well as TIV were employed. Significance threshold for these comparisons was set at voxel-wise $p < 0.05$ and cluster $p < 0.05$ with Gaussian Random Field (GRF) correction in whole-brain level.

Complementarily, a validating VBM analysis for the dataset conducted in the CAT12 was carried out in the FSL-PALM. The analysis was first with ANOVA, while followed up with a set of independent t-tests for group-paired comparisons. TFCE (5000 permutations)-FWE correction was also employed for the re-VBM-analysis.

2.7. Other analysis

Descriptive statistics were used to report demographic and clinical information, attention vigilance measures, and TIV, with χ^2 (Arunogiri et al., 2018) (for dichotomous variables), and *t* test or one-way ANOVA with Tukey's *pos-hoc* test (for continuous variables) for group comparisons. If a variable was highly skewed in distribution, Mann–Whitney U or Kruskal–Wallis H test was used instead.

Mean volume values in clusters obtained from the main ANOVA for brain images were further compared across groups with analysis of covariance (ANCOVA), sex, age, education, smoking, drinking and TIV set as controlling covariates. Sidark correction was used for multiple comparisons of *post-hoc* tests, with corrected $p < 0.05$ (two-tailed) considered to be significant.

Predictive factors of gray matter volume alterations were investigated with multiple regression analysis with stepwise selection (p-in = 0.05, p-out = 0.1) within regions of interest (ROI) in each patient group. MA use variables (age of first MA use, years of chronic use, duration of abstinence and ASI-drug), psychotic course and treatment variables (illness duration of psychosis, duration of antipsychotic treatment and current daily antipsychotic dose (quantified as chlorpromazine equivalent doses (AAPP et al., 2022; NHS Foundation Trust, 2009), see Supplemental table 1 for detailed information)), as well as other potential influential factors, including age, sex, education, smoking, drinking, other illicit drug ever used and TIV were included in the list of independent variables (as not applicable, psychotic course and treatment variables were exempted in analysis for the MA, while MA use variables and other illicit drug ever used were exempted in analysis for the SCZ). Volume measure (the value of mean volume) in each ROI was put as the single dependent variable respectively in any individual analysis. ROIs were significant clusters in the main ANOVA comparing brain images,

Table 1
Participant characteristics.

Variables	HC (n = 53)	MA (n = 22)	MAP (n = 34)	SCZ (n = 33)	Statistics[$] χ^2 or F or *t* or Z	p-value	multiple comparisons
Demographic							
Sex (male/ female)	41/12	19/3	30/4	25/8	2.61	0.455	–
Age (years), M ± SD	34.9 ± 8.9	39.2 ± 8.2	35.7 ± 6.8	31.2 ± 8.6	4.45	0.005	SCZ < MA
Education (years), M ± SD	12.2 ± 3.0	11.6 ± 3.0	10.7 ± 3.0	10.6 ± 3.0	2.71	0.047	No group-paired differences
Right handedness (yes/no)	47/6	20/2	30/4	32/1	2.07	0.559	–
Methamphetamine							
Age of first MA use (years), M ± SD	–	29.5 ± 9.0	27.1 ± 6.4	–	1.18	0.242	–
Duration of MA use (years)[a]					0.24	0.816	
M ± SD	–	4.0 ± 3.4	4.2 ± 2.7	–			–
Median (range)	-	2.5 (0.3–13.1)	3.5 (0.3–10.3)	-			
ASI-drug[b],	–			–			
M ± SD		0.024 ± 0.061	0.034 ± 0.061		1.82	0.070	–
Median (range)		0 (0–0.200)	0 (0–0.250)				
Duration of abstinence (months)[c]	–						
M ± SD	-	56.7 ± 47.7	33.9 ± 29.3	–	2.22	0.030	–
Median (range)		40.3 (1.4–222.0)	27.5 (0.6–141.6)	-	2.22	0.027	
Other substance							
Cigarette smoking (1 = not at all, 2 = less than one pack per day, 3 = at least one pack per day), M ± SD	1.38 ± 0.49	2.09 ± 0.61	2.24 ± 0.43	1.73 ± 0.84	16.78	0.000	MA, MAP & SCZ > HC MAP > SCZ
Alcohol drinking (1 = not at all, 2 = occasionally, 3 = often, 4 = at least 3 times per week), M ± SD	1.75 ± 0.55	2.59 ± 1.10	2.47 ± 1.08	1.39 ± 0.50	15.99	0.000	MA & MAP > HC & SCZ
Other illicit drug ever used[d] (yes/no)	0/53	7/15	12/22	0/33	0.07[c]	0.788	–
Psychosis course and treatment							
Illness duration (years)[e], M ± SD	–	–	5.20 ± 3.19	5.82 ± 5.62	0.55	0.582	–
Ever received antipsychotic medications (yes /no)[f]	0/53	0/22	18/16	33/0	20.40	0.000	–
Duration of antipsychotic treatment (month)[g], M ± SD	–	–	10.66 ± 10.25	45.56 ± 53.71	–	–	
Taking antipsychotics currently[h] (yes/no)	0/53	0/22	11/23	33/0	97.75	0.000	–
Current daily antipsychotic dose (chlorpromazine-equivalent doses, mg/day)[i], M ± SD	–	–	227.3 ± 110.4	283.3 ± 122.1	–	–	
Other psychotropic medications taken currently[j]							
Mood stabilizers (yes/no)	0/53	0/22	0/34	1/32	–	–	
Antidepressants (yes/no)	0/53	3/19	2/32	1/32	–	–	
Benzodiazepines (yes/no)	0/53	1/21	1/33	3/29	–	–	
TIV (ml), M ± SD	1447.3 ± 137.9	1470.2 ± 115.1	1447.9 ± 119.8	1414.0 ± 116.1	0.97	0.408	
Psychotic symptoms and attention vigilance							
Symptom severity (PANSS score)		–					
Positive, M ± SD	–	–	9.85 ± 6.91	19.73 ± 7.60	5.57	0.000	–
Negative, M ± SD	–	–	9.62 ± 6.24	14.94 ± 8.01	3.03	0.004	–
General psychopathology, M ± SD	–	–	22.82 ± 9.56	22.82 ± 9.56	5.24	0.000	–
Total, M ± SD	–	–	42.29 ± 19.93	70.39 ± 21.56	5.54	0.000	–
Current psychotic symptoms (with/without/ambiguous)[k]			6/28/0	26/4/3			
Attention vigilance (identification test performance)							
Accuracy, M ± SD	1.27 ± 0.39	1.13 ± 0.40	1.00 ± 0.49	0.98 ± 0.45	1.03	0.007	HC > MAP & SCZ
Speed, M ± SD	2.79 ± 0.09	2.77 ± 0.11	2.80 ± 0.11	2.82 ± 0.13	4.22	0.378	–

Note: [$] Chi-square tests were conducted for dichotomous variables; *t*-tests or one-way ANOVA with Tukey's post hoc tests were conducted for continuous variables, while if a variable was highly skewed in distribution, Mann–Whitney U or Kruskal–Wallis H test was applied instead; p-values were two-tailed, with $p < 0.05$ set to be significant. In the column of variables: [a] Duration of MA use refers to the total number of years from first MA use to the study interview, subtracting out months of continued abstinence within this time period; [b] ASI-drug is the drug use subscale score of ASI, assessing severity of drug use during one month before the study interview; [c] Duration of abstinence refers to the number of months from last time MA use to the study interview; [d] In the MA group, 4 participants had used heroin, 5 had used other opioids, and 3 used cannabis; in the MAP group, 10 had used cannabis, 1 had used cocaine, 3 used heroin and 1 other opioids; comparison for this variable was conducted between the MA and MAP; [e] Illness duration refers to time coverage between the onset of first psychotic symptoms and the study interview; [f] Comparative statistics were conducted only between the MAP and the SCZ; [g] Duration of antipsychotic treatment refers to the number of months an individual had taken antipsychotics before the study interview; data presented in the MAP were only for the 18 participants who had ever received antipsychotic medications; [h] Currently means during the month before the study interview; comparative statistics was conducted only between the MAP and the SCZ; [i] Current daily antipsychotic dose was quantified as chlorpromazine equivalent doses per day during the month prior to the study interview; data presented in the MAP were only for the 11 participants who were taking antipsychotics during the month before the study interview; [j] Other psychotropic medications refer to antidepressants, benzodiazepines and mood stabilizers; taken currently means taken by the participants during the month before the study interview; see more detailed information in Supplemental Table 1; [k] Subject with current psychotic symptoms defined as the PANSS-positive score ≥ 13, with at least two items for positive symptoms scored ≥ 3, while subject

without defined as the PANSS-positive score ≤ 9, whereas subjects ambiguous defined as the PANSS-positive scored between 10 and 12. Abbreviations: HC, healthy controls; MA, methamphetamine users without psychosis; MAP, patients with methamphetamine-associated psychosis; SCZ, patients with schizophrenia; ASI, Addiction Severity Index; TIV, total intracranial volume; PANSS, the Positive and Negative Syndrome Scale; M ± SD, mean ± standard deviation.

while with mean volume values altered from the HC in the specific group to be analyzed. In complementary, significant clusters in the *post-hoc* tests following ANOVA were also used as ROIs.

Associations of volume measures in each ROI with psychotic symptoms (PANSS scores) and attention impairment (identification test outcomes) were examined for both psychotic groups (the MAP and SCZ) respectively, applying partial correlation analysis with controlling for age, sex, education, smoking, drinking, current daily dose of antipsychotics and TIV. While analysis in the MAP were further controlled for ASI-drug to exclude acute effect of drug use. Significant level was set at two-tailed $p < 0.05$.

3. Results

3.1. Participant characteristics

As shown in Table 1, the 4 groups were matched in sex distribution. All patient groups (the MA, MAP and SCZ) matched the HC in age, while the SCZ were younger than the MA. Education years showed marginal group effect in ANOVA, while no group-pair differences in host-hoc tests.

The MAP had less abstinence months than the MA. All patient groups smoked severer than the HC, with the MAP severer than the SCZ in smoking. The MA and MAP consumed alcohol more frequently than the HC and SCZ respectively. Other illicit drugs had ever been used by 12 of the MAP and 7 of the MA.

Eighteen of the MAP and all participants in the SCZ had ever used antipsychotic medications, with11 MAP and all SCZ subjects taking antipsychotics currently. Other psychotropic medications, including antidepressants, benzodiazepines and mood stabilizers, were administered by a small number of clinical participants during the month before the study interview (see Supplemental table 1 for more detailed information).

The MAP had less severe psychotic symptoms than the SCZ, as reflected in all PANSS sub-scale scores as well as in the PANSS-total score. Twenty-eight of the 34 MAP participants actually showed no explicit psychotic symptoms at the time of interview. While both psychotic groups presented with poorer accuracy in identification test compared to the HC.

3.2. Gray matter volume comparisons

As shown in Fig. 1 and Table 2, eight clusters were found to be significant in the 4-group ANOVA of VBM analysis, which distributed mostly in the frontal cortex, with peak coordinates located in the left medial superior frontal gyrus, left middle frontal gyrus, orbital part of the right inferior frontal gyrus, right gyrus rectus, triangular part of the right inferior frontal gyrus, right precuneus, and orbital part of the right middle frontal gyrus, respectively; while one of the clusters was located in the left middle temporal gyrus (Fig. 1 A-C). When comparing volume measures within the clusters, both the MAP and the SCZ showed decreased mean volume in all the frontal clusters as well as all the frontal clusters combined when compared to the HC, whereas the SCZ further had lower mean volume than the HC in the temporal cluster (Fig. 1 D). Relative to the HC, the MA showed an overall trend of mean volume decrease, while only marginally significant (at the level $p < 0.05$) in two small clusters in the right orbital and triangular part of inferior frontal gyrus.

Post-hoc tests following the main ANOVA in VBM analysis showed that compared with the HC, the MA had decreased gray matter volume in two very small clusters (cluster size < 70 voxels each) in the left medial superior frontal gyrus, which were also involved in the brain regions affected in the MAP, while the MAP exhibited a much more extended cluster (cluster size = 4229 voxels) with reduced gray matter volume in the frontal cortex, prefrontal in particular, with peak coordinates in the left medial superior frontal gyrus. The SCZ showed the most extensive gray matter decrease among the patient groups, with affected brain regions encompassing the frontal and temporal lobes, while they were overlapped with the MAP in gray matter decrease in the frontal cortex (Fig. 1 B-C). No other group-pair differences in gray matter volumes were detected out.

3.3. Predictive factors of gray matter reductions in patient groups.

Regression analyses found that in the MAP, duration of abstinence was a predictor of gray matter volume in three affected clusters, with longer periods of abstinence associated with greater mean volumes. Similar predictive effect also presented in one affected cluster in the MA, while with marginal significant level (Fig. 2, see Supplemental table 3 for more detailed data). Illness duration of psychosis also showed an effect on the volume values of the affected regions in the MAP as well as in the SCZ, with longer duration predicting smaller mean volumes in some of the ROIs (Fig. 3, see Supplemental table 3 for more detailed data).

Antipsychotic treatment duration was also a predictor of gray matter volume among affected regions in the SCZ, with longer duration of antipsychotic treatment associated with lower gray matter volumes (Fig. 4, see Supplemental table 3 for more detailed data); while antipsychotic treatment variables were not predictive in the MAP, either by regression analysis within ROIs (Supplemental table 3) or through VBM analysis comparing gray matter volumes between subgroups among the MAP (subjects ever received antipsychotics vs subjects ever not, and subjects taking antipsychotics currently vs subject currently not, respectively; data were not shown for negative findings).

Additionally, TIV and age was revealed to relate to regional gray matter volumes positively and negatively respectively in the SCZ and the MA; whereas MA use duration was associated with greater volume in one affected region in the MAP (see Supplemental table 3).

3.4. Associations of volume measures with psychotic symptoms and attention impairment

Correlations were not shown to be significant between psychotic symptoms (PANSS and its subscale scores) and regional gray matter volumes in any ROIs or in ROIs combined in both psychotic groups respectively (data not shown). Subgroup comparisons among the MAP between participants with and without current psychotic symptoms also didn't show any regional gray matter volumes that were associated with psychotic symptoms.

Volume reductions were associated with attention impairment (accuracy decrease in identification test performance) in the SCZ in most affected brain regions (Fig. 5 A), while a reversed association was observed in the MAP in frontal cortex (Fig. 5 B).

3.5. Validating VBM analysis

With the same dataset for VBM analysis, brain alterations in gray matter volume in the patient groups resulted from FSL-PALM (Fig. 6) were quite similar to those derived from CAT12 (see Fig. 1), while regional gray matter volumes were not altered in the MA when compared to healthy controls.

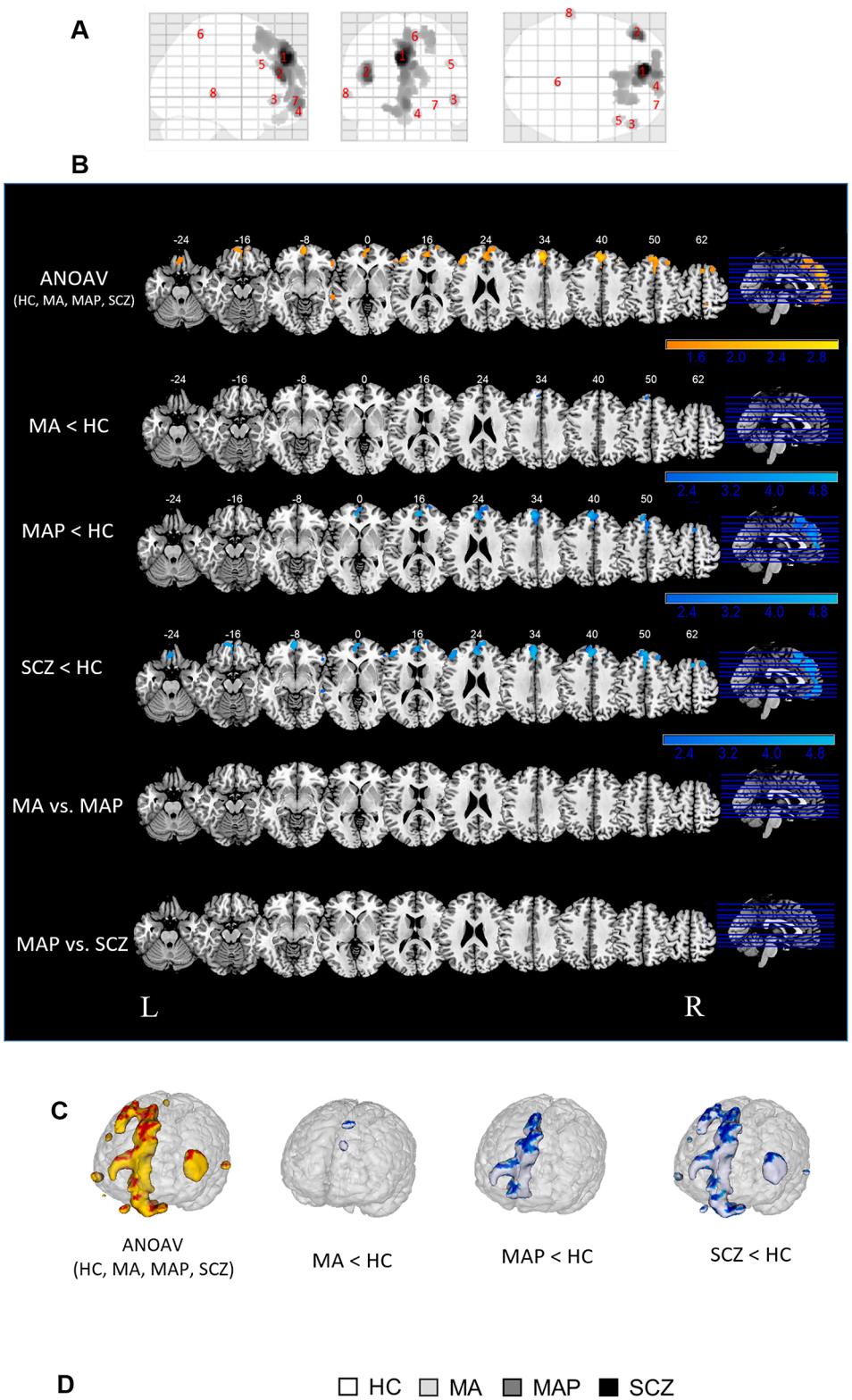

Fig. 1. Regions with gray matter volume different among the HC, MA, MAP and SCZ. Significant clusters were resulted from 4-groups ANOVA for whole-brain gray matter volume comparison and its post-hoc group-pair tests in VBM analysis, while controlling for sex, age, education, smoking, drinking and TIV. TFCE (5000 permutations) with family-wise error (FWE) was employed to correct for multiple tests. Significance was thresholded at TFCE-FWE corrected voxel-wise $p < 0.05$ with cluster size > 10. HC: healthy controls (n = 53); MA: MA users without psychosis (n = 22); MAP: patients with MA-associated psychosis (n = 34); SCZ: patients with schizophrenia (n = 33). **A.** Significant clusters obtained from the 4-groups ANOVA, presented in glass brain view (sagittal, coronal and axial respectively) and numbered as the same as in Table 2. Gray intensity represents significant levels. The region of peak coordinates located in for each cluster: 1: left medial superior frontal gyrus; 2: left middle frontal gyrus; 3: right inferior frontal gyrus, orbital part; 4: right gyrus rectus; 5: right inferior frontal gyrus, triangular part; 6: right precuneus; 7: right middle frontal gyrus, orbital part; 8: left middle temporal gyrus. **B.** Significant clusters obtained from the 4-groups ANOVA and its post-hoc group-pair tests, presented in axial brain slices. ANOVA (HC, MA, MAP, SCZ): regions with gray matter volume showed group effects in the ANOVA; MA < HC: regions with gray matter volume decreased in the MA when compared to the HC in post-hoc tests; MAP < HC: regions with gray matter volume decreased in the MAP when compared to the HC in post-hoc tests; SCZ < HC: regions with gray matter volume decreased in the SCZ when compared to the HC in post-hoc tests; MA vs MAP: no region was significantly different in post-hoc comparisons between the MA and MAP; MAP vs SCZ: no region was significantly different in host-hoc comparisons between the MAP and SCZ. MA vs SCZ: no region was significantly different in post-hoc comparisons between the MA and SCZ. Regions of significance were colored; Numbers upper the brain slices were z coordinates in MNI space; Color-bars with values underneath denote -log p-value. L: left side of the brain; R: right side of the brain. **C.** Significant clusters obtained from the 4-groups ANOVA and its post-hoc group-pair tests, rendering into brain surface. ANOVA (HC, MA, MAP, SCZ): regions with gray matter volume showed group effects in the ANOVA; MA < HC: regions with gray matter volume decreased in the MA when compared to the HC in post-hoc tests; MAP < HC: regions with gray matter volume decreased in the MAP when compared to the HC in post-hoc tests; SCZ < HC: regions with gray matter volume decreased in the SCZ when compared to the HC in post-hoc tests; Regions of significance were coloured. **D.** Comparisons of volume measure (mean volume value) in significant clusters obtained from the 4-groups ANOVA. Left: Comparisons between groups in mean volume in each cluster, respectively; Numbers in the X-axis represent clusters numbered as the same in panel A. Right: Comparisons between groups in mean volume in all the frontal clusters combined (the combination of cluster 1–7 numbered in panel A). Volume measure was presented by bar plot with mean ± standard error (SE). Comparisons across groups were conducted with univariate ANCOVA followed by Sidark post-hoc tests, with sex, age, education, smoking, drinking and TIV being controlled for as nuisance covariates. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2
Brain clusters resulted from VBM analysis showing gray matter volume different among the HC, MA, MAP, and SCZ.

Cluster No.	L/R	Lobe	Gyrus	Region	Peak MNI coordinates (x y z)	K_E	$P_{FWE-corr}$	$P_{FDR-corr}$	P_{uncorr}	TFCE value	BA
ANOVA (HC, MA, MAP, SCZ)											
1	L	Frontal	Medial Frontal Gyrus	Medial superior frontal gyrus	−3 47 35	6492	0.001	0.002	0.000	15382.47	9, 8, 10, 11, 6, 32
2	L	Frontal	Middle Frontal Gyrus	Middle frontal gyrus	42 38 21	928	0.004	0.002	0.000	12159.24	46, 10
3	R	Frontal	Inferior Frontal Gyrus	Inferior frontal gyrus, orbital part	51 35 –5	213	0.024	0.002	0.000	8005.68	47
4	R	Frontal	Medial Frontal Gyrus	Gyrus rectus	11 59 –18	67	0.036	0.002	0.000	7075.44	10
5	R	Frontal	Middle Frontal Gyrus	Inferior frontal gyrus, triangular part	44 24 30	65	0.037	0.002	0.000	7013.55	9
6	R	Frontal	Paracentral Lobule	Precuneus	8 –47 58	52	0.034	0.002	0.000	7020.09	5
7	R	Frontal	Superior Frontal Gyrus	Middle frontal gyrus, orbital part	30 60 –9	10	0.049	0.002	0.000	6417.56	11
8	L	Temporal	Middle Temporal Gyrus	Middle temporal gyrus	−65 –32 0	116	0.032	0.003	0.000	7376.85	46, 10
MA < HC											
a	L	Frontal	Medial Frontal Gyrus	Medial superior frontal gyrus	−9 45 33	61	0.040	0.037	0.000	247.92	9
b	L	Frontal	Medial Frontal Gyrus	Medial superior frontal gyrus	−9 42 50	67	0.042	0.053	0.001	240.94	8
MAP < HC											
a'	L	Frontal	Medial Frontal Gyrus	Medial superior frontal gyrus	−3 47 21	4229	0.000	0.001	0.000	1050.78	9, 10, 8, 6, 32
SCZ < HC											
I	L	Frontal	Medial Frontal Gyrus	Anterior cingulate and paracingulate gyri	3 38 27	6481	0.000	0.000	0.000	1506.10	8, 9, 10,11, 6, 32
II	L	Frontal	Middle Frontal Gyrus	Middle frontal gyrus	−44 39 20	928	0.000	0.000	0.000	969.63	46, 10
III	R	Frontal	Inferior Frontal Gyrus	Inferior frontal gyrus, orbital part	50 35 –3	117	0.000	0.000	0.030	187.17	47
IV	R	Frontal	Superior Frontal Gyrus	Gyrus rectus	11 57 –18	35	0.000	0.000	0.031	185.48	–
V	R	Frontal	Middle Frontal Gyrus	Inferior frontal gyrus, triangular part	44 24 30	38	0.000	0.000	0.037	167.29	9
VI	L	Temporal	Middle Temporal Gyrus	Middle temporal gyrus	−65 –32 0	43	0.000	0.000	0.040	159.14	21, 22

Note: Significant clusters were resulted from 4-groups ANOVA for whole-brain gray matter volume comparison and its according post-hoc group-pair tests in VBM analysis, while controlling for sex, age, education, smoking, drinking and TIV. TFCE (5000 permutations) with family-wise error (FWE) was employed to correct for multiple tests. Significance was thresholded at TFCE-FWE corrected voxel-wise $p < 0.05$ with cluster size > 10. All data was corresponded to Fig. 1, while negative results were not shown in the table. L/R: left (L) or right (R) side of the brain that the cluster primarily located in; Lobe: brain lobe that the cluster primarily located in; Gyrus: brain gyrus that the cluster primarily located in; Region: the specific region of peak coordinates located in, labeled with the automated anatomical atlas 3 (AAL3); MNI: the Montreal Neurological Institute coordinate system; K_E = number of continued voxels; $P_{FWE-corr}$: FWE-corrected p-value; $P_{FDR-corr}$: FDR-corrected p-value; P_{uncorr}: uncorrected p-value; BA: Brodmann's areas that the cluster was involved in; HC: healthy controls (n = 53); MA: methamphetamine users without psychosis (n = 22); MAP: patients with MA-associated psychosis (n = 34); SCZ: patients with schizophrenia (n = 33).

4. Discussion

To our knowledge, this is the first study comparing patients with MA-associated psychosis in parallel with schizophrenia patients, MA users without psychosis and healthy controls in brain alterations. This current study demonstrated that patients with MA-associated psychosis had similar gray matter decrease in the frontal cortex as patients with schizophrenia, while schizophrenia individuals showed more extensive gray matter loss than patients with MA-associated psychosis. This suggests the two psychotic conditions could share common neuropathology in the frontal cortex, although they might be differed in overall mechanisms.

It is interesting that gray matter reductions in the psychotic groups distributed mainly in prefrontal regions, where the dopamine projections arisen from the ventral tegmental area (VTA) of midbrain are concentrated. A critical action of dopamine on its targets is modulating glutamate transmission (Gardoni and Bellone, 2015). Glutamatergic projections from cortex in turn repress dopamine release from the VTA to limbic area with a top-down control manner (Jauhar et al., 2018). In the perspective of neural circuitry, acute exposure to MA would foster excessive dopamine release. Excessive dopamine within synaptic clefts in long-term is neural toxic (Jan et al., 2012), and cortical neurons could be damaged under this neurotoxicity (Hsieh et al., 2014; Jan et al., 2012; Yamamuro et al., 2015). As a consequence of cortical neuronal damage, glutamate projected downward from the cortex would be dysregulated, leading to a disinhibition of mesolimbic dopaminergic activity (Tost et al., 2010). In light of this thinking, gray matter reductions in patient's frontal cortices may reflect a pathological state of neuronal cell death in the cortical dopaminoceptive areas. Positive symptoms in the patients with MA-associated psychosis during their abstinence could be generate from a secondary hyperactivity of the mesolimbic dopaminergic pathway (Pletnikov and Waddington, 2015). This perspective provides an explanation why psychotic symptoms associated with MA use protracted long or recurred spontaneously after the drug has been quit, and the dopamine receptor antagonists are effective for this condition during the patient's abstinence (Chiang et al., 2019; Grant et al., 2012). However, as cross-sectional study in nature, the observed reduced gray matter volumes in MA use patients could alternatively represent pre-existed brain deficits predisposing psychosis development. Longitudinal studies are warranted to further explain the mechanisms.

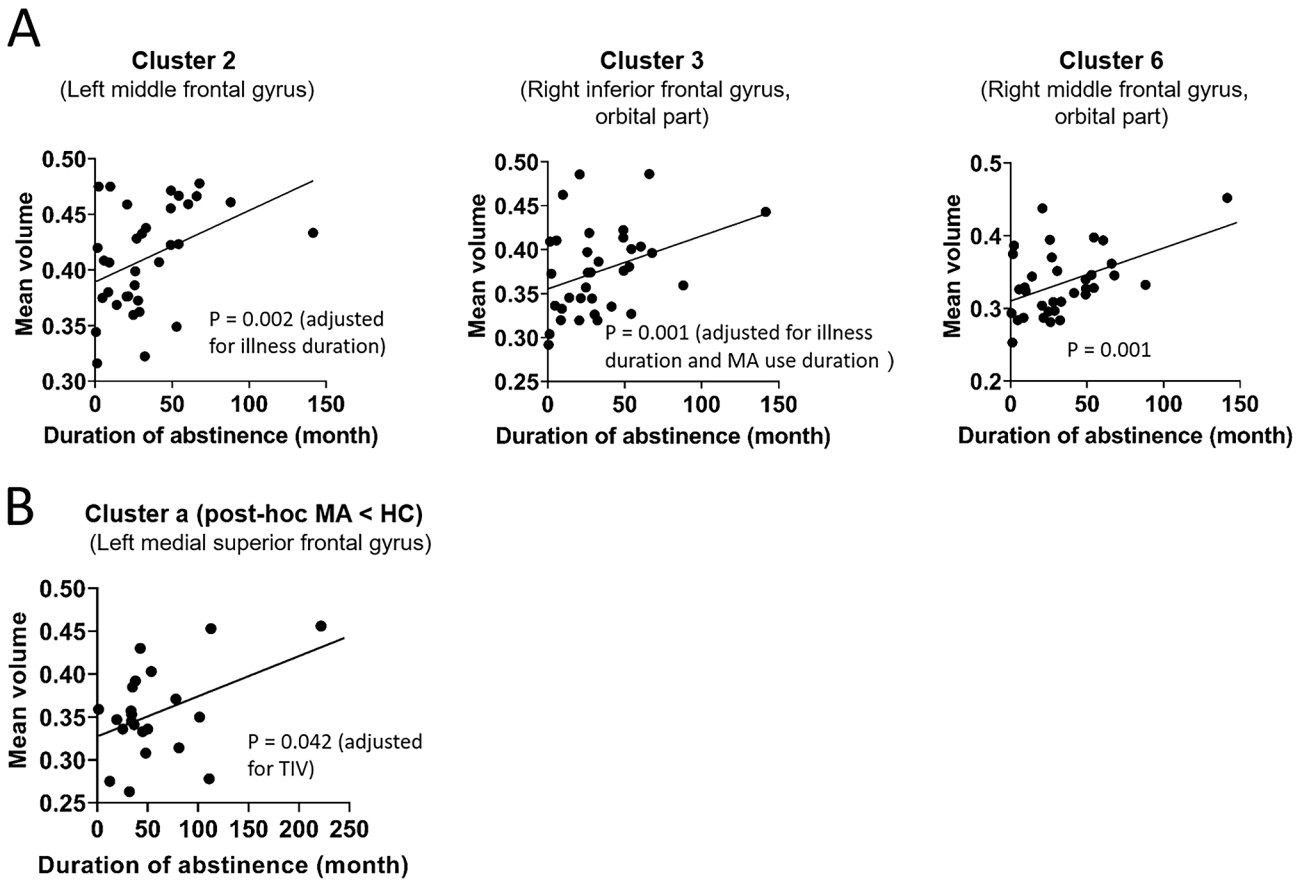

Fig. 2. Regression lines indicating predictive effects of abstinence duration on regional volume measures in the MAP (**A**) and in the MA (**B**), respectively. Clusters were numbered as the same in Table 2. See Supplemental table 3 for more detailed data.

In this current study, the MA users without psychosis showed a general trend but not significant gray matter decrease in clusters that were affected in the psychotic groups. While two very small clusters in the right superior frontal gyrus reached significance when compared to the healthy controls in post-hoc analyses after the ANOVA, these significances were not replicated in the validating VBM analysis with FSL-Palm. MA users had often been reported to have reduced cortical volumes than did control individuals (Hall et al., 2015) (London et al., 2015). However, multiple of the studies did not excluded patients with MA-associated psychosis from MA users without psychosis (London et al., 2015). Addiction is conceptualized as a disorder of neuroplasticity with long-lasting adaptive neural changes. Keeping this conception in mind, it sounds also reasonable that the MA use subjects without comorbidities had no apparent brain damages. However, chronic MA exposure would still exert adverse effects on the brain. The trend or marginal level of gray matter reductions in the MA are noteworthy, as this could implicate a trend of neuropathology toward psychosis development.

We had previously reported ketamine chronic users showed gray matter reduced in the frontal cortex, specifically in the superior and middle frontal gyrus (Liao et al., 2011). The frontal cortical reductions were also found to be associated with total lifetime consumption of ketamine (Liao et al., 2011). As a competitive *N*-methyl-D-aspartate (NMDA) antagonist, ketamine has been shown to increase presynaptic glutamate, and excessive glutamate is with excitotoxicity to neuronal cells (Liao et al., 2011). This previous study together with ours currently indicated that different psychoactive drugs would exert similar adverse effects on the brain, although they could work through differential pathways; and frontal cortices could be more vulnerable to drug effects than other brain portions. In addition, glutamatergic neurotransmission could also be crucial in mechanisms of psychosis development (McCutcheon et al., 2020).

Gray matter reductions in the frontal and temporal regions in our schizophrenia participants have been supported by multiple previous studies (Honea et al., 2005) (Kuperberg et al., 2003; Haijma et al., 2013). For example, Kuperberg et al. (Kuperberg et al., 2003) had demonstrated that patients with chronic schizophrenia displayed widespread cortical thinning that particularly affected the prefrontal and temporal cortex. Gray matter reductions in the schizophrenia participants were associated with longer illness course and older in age, as well as smaller TIV, which implicate a combination of aberrant neurodevelopmental process (reflected by the relationship of TIV with regional volumetric reductions) and illness progressions (illness course and age-related regional gray matter reductions) in the neuropathological changes of schizophrenia (Haijma et al., 2013; Shenton et al., 2001; Cropley et al., 2017; Nenadic et al., 2012). Medication factors, antipsychotic treatment duration in particular, was also related to regional gray matter reductions in the schizophrenia patients in our current study. The role of antipsychotics play in brain morphometry remains controversial, while several large-sample longitudinal studies (Ho et al., 2011; Veijola et al., 2014; Yang et al., 2021), and a recent large-sample real-world study (Chen et al., 2021) had demonstrated a subtle but significant antipsychotic-related gray matter decrease in the patients with schizophrenia.

Moreover, this current study exhibited a stepwise extension of gray matter loss across the MA – MAP – SCZ (from the HC to MA, then to the MAP, and lastly to the SCZ) as compared to the HC. The MAP and SCZ actually did not differ in gray matter volumes when comparing these two groups directly. Such findings could implicate a continuum of neuropathological progression between MA use and schizophrenia,

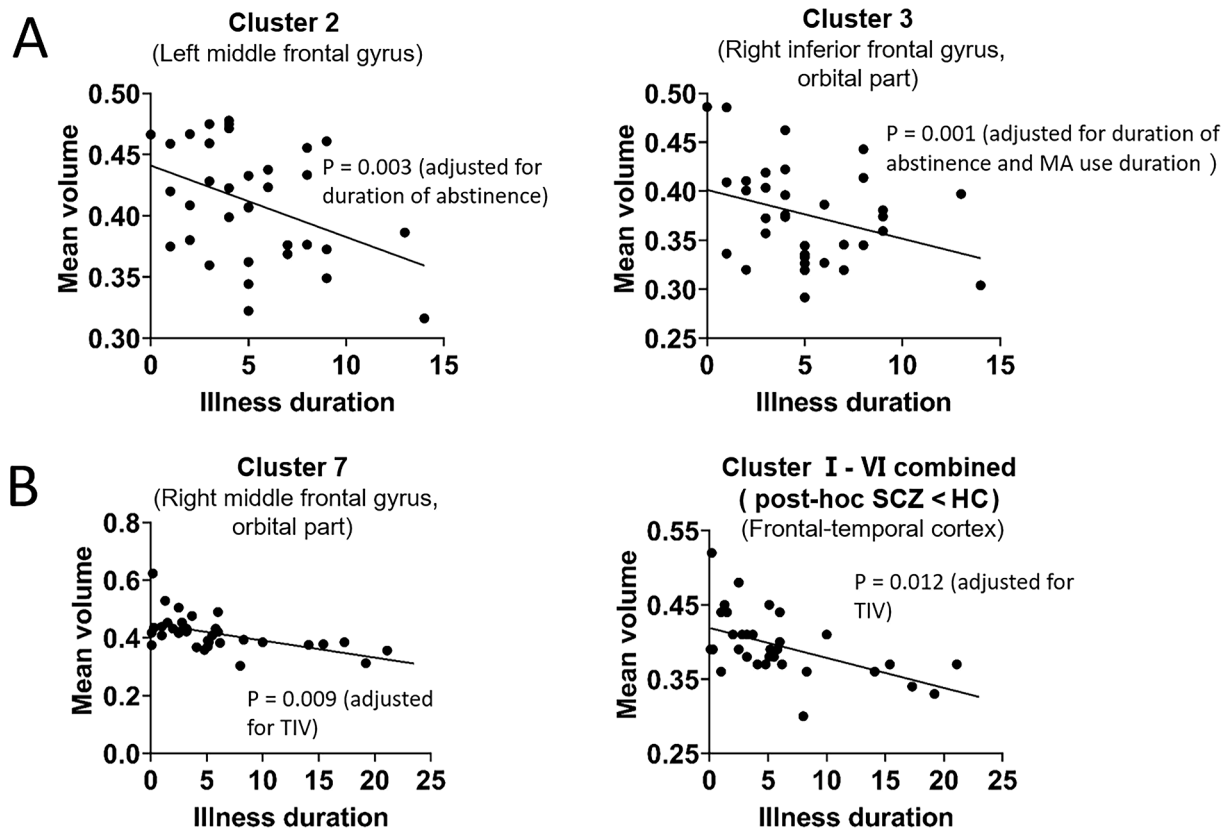

Fig. 3. Regression lines indicating predictive effects of illness duration of psychosis on regional volume measures in the MAP (**A**) and in the SCZ (**B**), respectively. Clusters were numbered as the same in Table 2. See Supplemental table 3 for more detailed data.

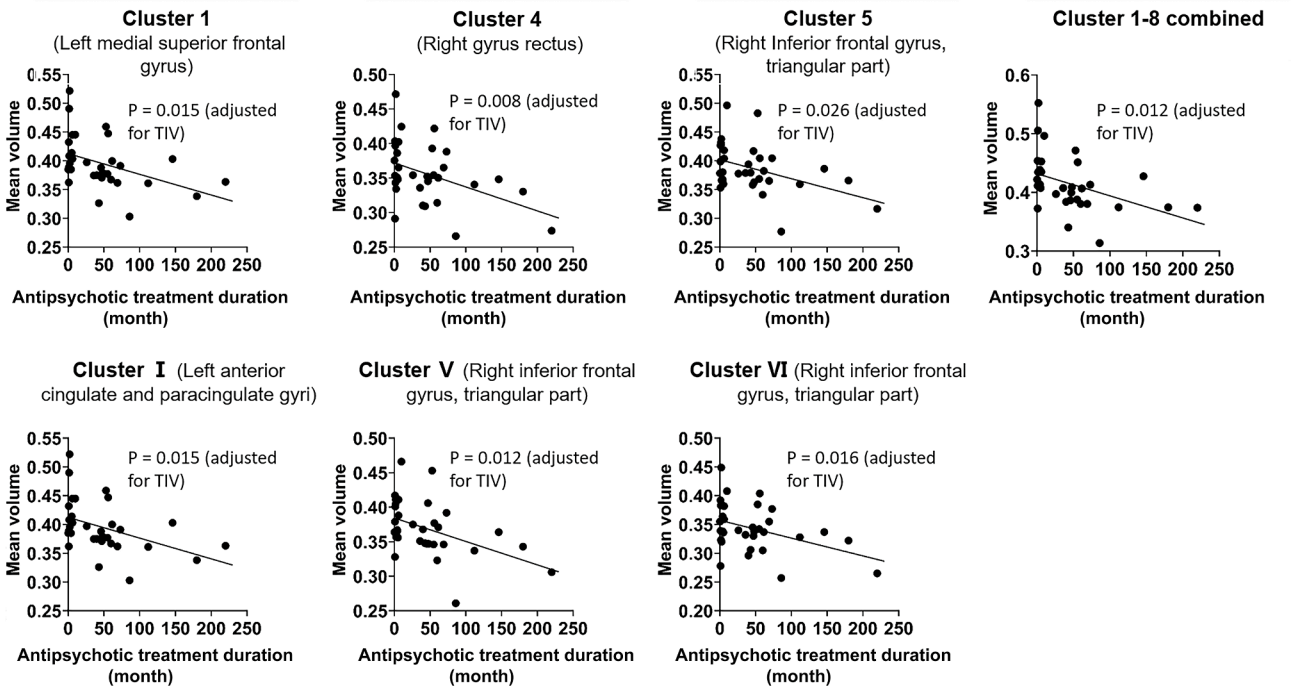

Fig. 4. Regression lines indicating predictive effects of antipsychotic treatment duration on regional volume measures in the SCZ. Clusters were numbered as the same in Table 2. See Supplemental table 3 for more detailed data.

where brain alterations in the MAP could represent a lighter endophenotype of psychosis disorder. Corresponding to its brain alteration, the MAP also had lighter psychotic symptoms than the SCZ. A recent study by Alexander et al. (Alexander et al., 2019) has supported this, by demonstrating less severe symptoms in subjects with stimulant-induced psychosis than schizophrenia patients. It is difficult to say how MA work

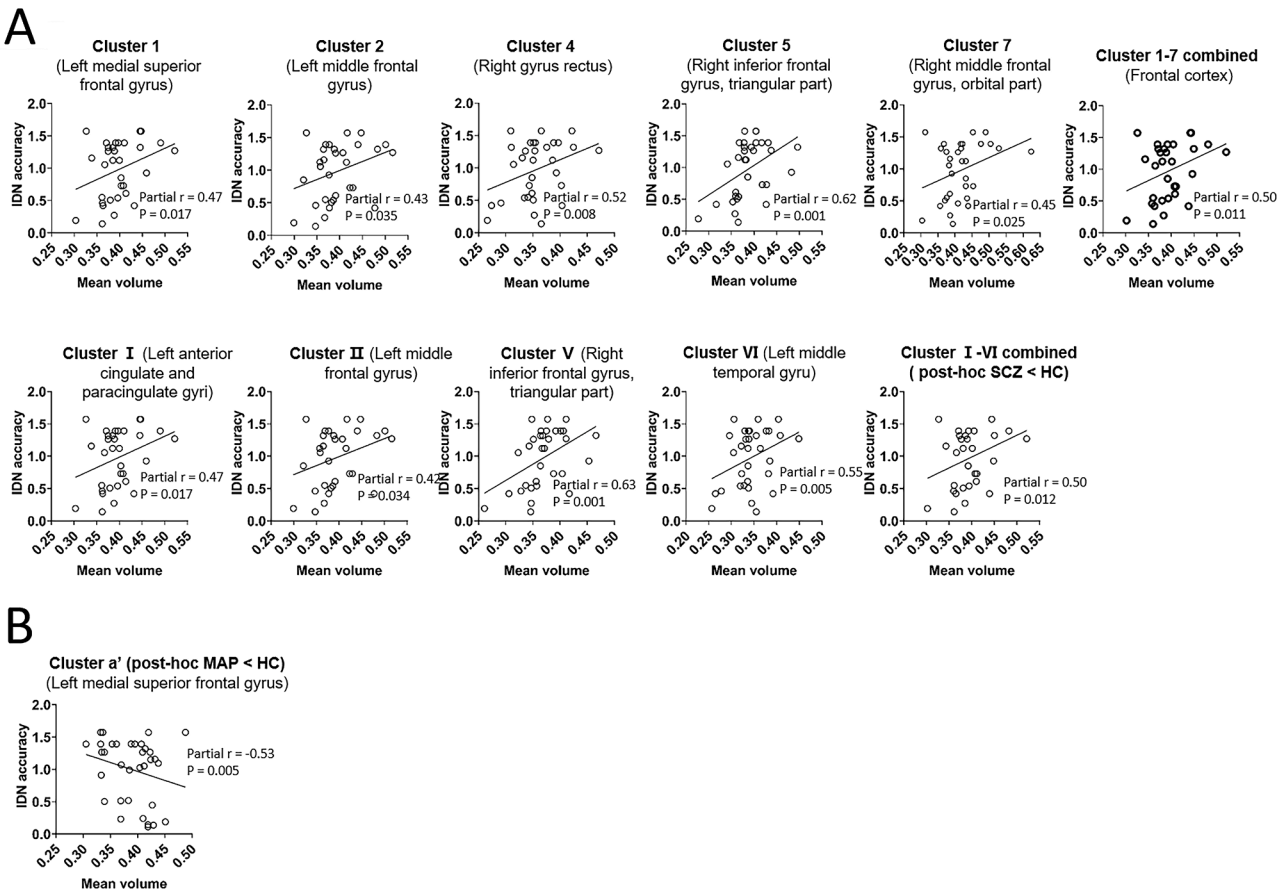

Fig. 5. Associations of mean volumes in ROIs with accuracy of identification test in the SCZ (**A**) and the MAP (**B**) respectively. The associations were examined by partial correlation analysis while controlling for age, sex, education, smoking, drinking, current daily antipsychotic dose and TIV, with significant findings ($p < 0.05$) to be presented. Clusters were numbered as the same in Table 2. IDN, identification test.

on the progression of neuropathology, with primary effects or alternatively, based on a secondary hit. And etiology underlying the observed brain alterations could heterogenous between the drug related and primary psychoses. However, these two psychotic conditions could be essentially homogenous in neuropathological process. While caution should be carefully taken when interpretating the observed findings, for this current study could not tease out effects of antipsychotic medications, as well as variability of drug use indices on the brain's morphometry.

Gray matter abnormalities were not explicitly observed in subcortical brain regions in any of our patient groups. Previous studies had often reported volume augmentations in striatal regions in both MA use and schizophrenia population (London et al., 2015; Okada et al., 2016; van Erp et al., 2016). For example, volume enhancements had been reported in the caudate, putamen and pallidum respectively in both patients (London et al., 2015; Okada et al., 2016); (van Erp et al., 2016). However, findings in previous study are sometimes heterogeneous. In agreement with ours, Zhang et al.'s (Zhang et al., 2018) study also didn't show subcortical alterations in both the patients with MA-associated psychosis and the schizophrenia individuals. Contrary to usual reports, Farnia et al. (Farnia et al., 2020) demonstrated in their study that patients with MA-associated psychosis had decreased volume in left caudate, whereas schizophrenia individuals had volume decrease in left putamen. Variability in subject characteristics between studies, such as differentiations in drug use and abstinence duration, illness course and treatment experience, could account partly for the diversity of study findings. Furthermore, methodological discrepancy among VBM studies, such as different sizes in smoothing kernel, linear versus affine in automated preprocess and varied correction methods for p-value, could also contribute to finding's variability.

In behavioral aspect, impairment of attention vigilance is assumed to be a core cognitive abnormality in schizophrenia (Klein et al., 2020). Patients with schizophrenia generally demonstrate poor vigilance in sustained attention tasks (Klein et al., 2020). Several brain regions in the cortex are thought to be relevant to attention vigilance, including prefrontal and right frontal cortices, and the inferior parietal and superior temporal gyri (Wikipedia, 2021; Sani et al., 2021). In this current study, patients with MA-associated psychosis presented with impaired attention vigilance (reduced accuracy in identification test) as those patients with schizophrenia, also suggesting a resemblance of underlying neuropathology in both disorders. Meanwhile, decreased gray matter volumes, particularly in the frontal lobe, were associated with decreased attentional vigilance in the SCZ, whereas a reversed association was observed in the MAP in the frontal cortex. These findings support a corresponding relationship of the frontal areas with attention vigilance. The negative correlation between regional gray matter volume and attention vigilance in the MAP might be due to pathological gliosis after the cortical impairment. Literatures have supported a linkage between activity in the frontal cortex and attentional performance in MA use individuals (London et al., 2015). For example; Fassbender and colleagues (Fassbender et al., 2015) demonstrated in their study that the healthy subjects, non-psychotic MA users and subjects with MA-associated psychosis showed different relationships between the prefrontal activity and intraindividual variability of reaction time to incongruent stimuli on Stroop task.

Additionally, the cortical morphology appeared to be amended with protracted abstinence in MA use individuals, reflecting by the observation that longer abstinence length predicted regional gray matter

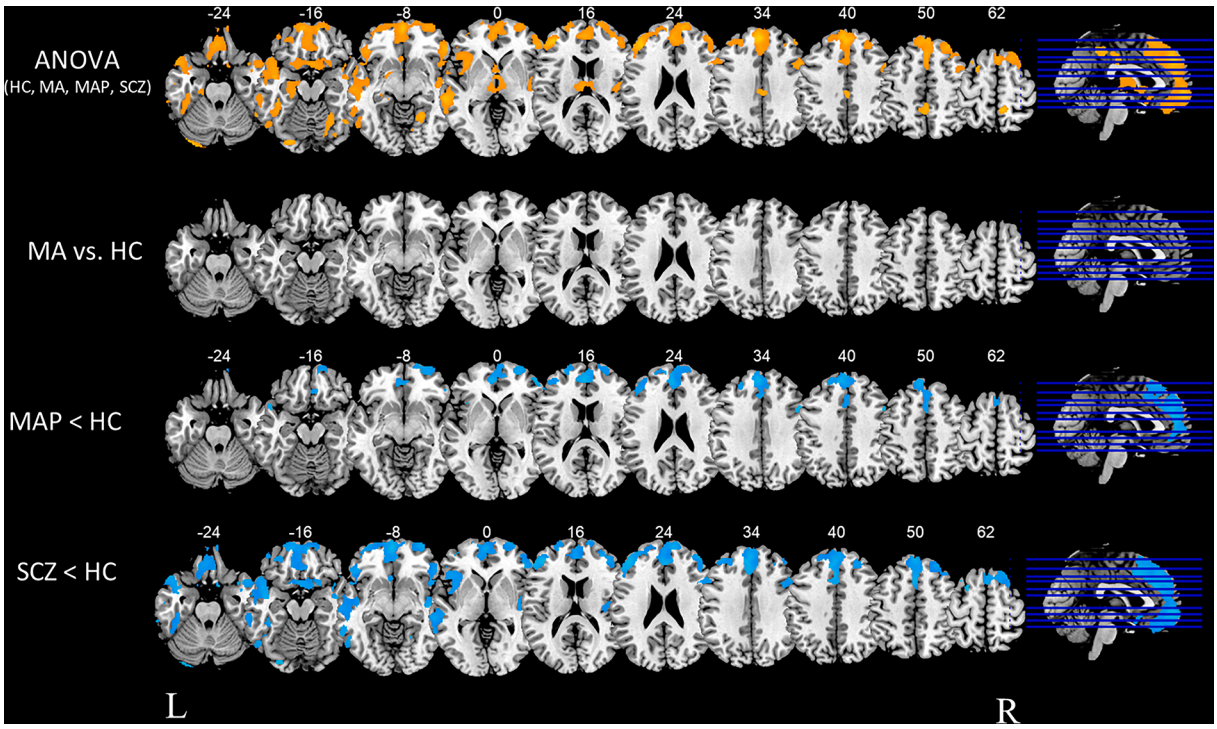

Fig. 6. Validating VBM analysis with FSL-PALM showing gray matter volume different among the HC, MA, MAP and SCZ. ANOVA (HC, MA, MAP, SCZ): regions with grey matter volume different across the 4 groups obtained from ANOVA. MA vs HC: no region was significantly different in gray matter volume between the MA and the HC; MAP < HC: regions with gray matter volume decrease in the MAP compared to the HC; SCZ < HC: regions with gray matter volume decrease in the SCZ compared to the HC. Comparisons were conducted with the FSL-PALM by 4-groups ANOVA followed by a set of independent *t*-tests for group-pair comparisons, controlling for age, sex, education, smoking, drinking and TIV. Significance thresholded at TFCE-FEW corrected $p < 0.05$ (two-tailed). Significant regions were coloured. Numbers upper the axial brain maps were z coordinates in MNI space. Abbreviations: HC, healthy controls (n = 53); MA, MA users without psychosis (n = 22); MAP, patients with MA-associated psychosis (n = 34); SCZ, patients with schizophrenia (n = 33); L, left side of the brain; R, right side of the brain.

volume recovery in affected regions in the MAP whereas marginally in the MA. However, this morphological amendment was not accompanied with symptom remissions. With this end, the apparent amendment on brain morphometry with abstinence persistence might not represent neuropathological improvement, but could implicate a possible ineffective glial proliferation after the neuronal loss. Thinking with this way, the paradoxical negative association between MA use duration and brain volumes in affected regions in the MAP, as well as the negative association of regional gray matter volume with attention vigilance in this specific group could both reflect this type of glial repairment. Two studies recently had also reported gray matter volumes reverse with abstinence persistence, however regrettably, both studies did not investigate the association of recovery in brain structure with alleviation in clinical symptoms (Ruan et al., 2018; Nie et al., 2020).

Furthermore, illness duration of psychosis also showed predictive effect on regional gray matter reductions in both the MAP and SCZ (Fig. 3). As mentioned above, studies on brain imaging have supported an association of gray matter reduction with longer illness duration in schizophrenia, which implicates a progression of neuropathology in the disorder (Haijma et al., 2013). It is the first time to report this association also existed in patient with MA-associated psychosis, this association in both psychotic disorders could further implicate similar progressions of neuropathology underpinning both psychoses, although they could be different in the progression stages. It is difficult to explain this observation with purely drug effects; some other factors currently unclear could contribute to the neuropathological progressions.

Taken together, this study contributed to the research field of psychosis by indicating that both the psychotic disorders—the primary and the secondary to MA use—have common neuropathology in the frontal cortex. Moreover, a stepwise extension of gray matter reductions was exhibited across the MA – MAP – SCZ in our current study, implicating tentatively a continuum of neuropathology between MA use and schizophrenia.

Furthermore, in this current study, illness duration was shown to be among the predictive factors of regional gray matter reductions in MA-associated psychosis as well as in schizophrenia. Abstinence duration was found to be associated with volumetric recovery in affected regions in the MAP, however this amendment in brain morphometry was not accompanied with symptom's remission. These findings further suggested illness progression and ineffective glial repairment could be both involved in the process of neuropathological changes in MA-associated psychosis. Regional gray matter volume decrease was not associated with psychotic symptoms, but positively correlated with attentional impairment in the SCZ and negatively correlated with the attentional impairment in the MAP, particularly in the frontal cortex, supporting a close relationship of the frontal areas with cognitive functions.

The major strength of this study is the direct comparisons across four groups in parallel, with participants encompassing patients with MA-associated psychosis, patients with schizophrenia, nonpsychotic MA users, as well as healthy controls. Additionally, a validating VBM analysis with other software replicated the main results of brain alterations.

However, several limitations should be taken when interpreting the study results. First of all, due to the cross-sectional design, findings in this current study could not be inferred as any causality in a strict sense. The second limitation is a relatively modest sample size in the current study, which could weaken statistical power and therefore increase the possibility of getting false negative findings. Subcortical alterations could otherwise be observed in the clinical groups if more subjects could be involved in. Thirdly, the groups were not well matched in terms of age, education, smoking, drinking, and severity of psychotic symptoms, which could affect our data's comparability. We did control potential confounding variables in the study analyses, however better designed

research employing matched groups could result in more robust findings. Moreover, variations in drug use indices (such as MA use duration, abstinence duration and drug use severity evaluated by ASI-drug) were large among MA use participants in the study. Such variations enlarged within-group heterogeneities, enhancing the probability of getting false negative results in between group comparisons. However, nevertheless, this current study provided preliminary evidence indicating MA-associated psychosis and schizophrenia had an overlapped neuropathology reflected by gray matter loss in the frontal cortex.

CRediT authorship contribution statement

Xiaojian Jia: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Jianhong Wang:** Validation, Formal analysis, Investigation, Resources. **Wentao Jiang:** Validation, Formal analysis, Investigation, Resources. **Zhi Kong:** Validation, Formal analysis, Investigation, Resources. **Huan Deng:** Software, Formal analysis, Visualization. **Wentao Lai:** Validation, Formal analysis, Investigation, Resources. **Caihong Ye:** Validation, Formal analysis, Investigation, Resources. **Fen Guan:** Investigation. **Peng Li:** Writing – review & editing. **Min Zhao:** Conceptualization, Methodology. **Mei Yang:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

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The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103259.

References

Alexander, P.D., Gicas, K.M., Cheng, A., Lang, D.J., Procyshyn, R.M., Vertinsky, A.T., Panenka, W.J., Thornton, A.E., Rauscher, A., Wong, J.Y.X., Chan, T., Jones, A.A., Vila-Rodriguez, F., Honer, W.G., Barr, A.M., 2019. A comparison of regional brain volumes and white matter connectivity in subjects with stimulant induced psychosis versus schizophrenia. Psychopharmacology 236 (12), 3385–3399.

Aoki, Y., Orikabe, L., Takayanagi, Y., Yahata, N., Mozue, Y., Sudo, Y., Ishii, T., Itokawa, M., Suzuki, M., Kurachi, M., Okazaki, Y., Kasai, K., Yamasue, H., 2013. Volume reductions in frontopolar and left perisylvian cortices in methamphetamine induced psychosis. Schizophr. Res. 147 (2-3), 355–361.

Arunogiri, S., Foulds, J.A., McKetin, R., Lubman, D.I., 2018. A systematic review of risk factors for methamphetamine-associated psychosis. Austral. New Zealand J. Psychiatry 52 (6), 514–529.

The American Association of Psychiatric Pharmacists (AAPP)/College of Psychiatric and Neurologic Pharmacists (CPNP). Psychiatric pharmacy essentials: antipsychotic dose equivalents. AAPP. https://cpnp.org/guideline/essentials/antipsychotic-dose-equivalents (accessed Aug 1, 2022).

Chen, C., Hsu, F.C., Li, C.W., Huang, M.C., 2019. Structural, functional, and neurochemical neuroimaging of methamphetamine-associated psychosis: A systematic review. Psychiatry Res. Neuroimag. 292, 23–31.

Chen, Y., Womer, F.Y., Feng, R., Zhang, X., Zhang, Y., Duan, J., Chang, M., Yin, Z., Jiang, X., Wei, S., Wei, Y., Tang, Y., Wang, F., 2021. A real-world observation of antipsychotic effects on brain volumes and intrinsic brain activity in schizophrenia. Front. Neurosci. 15, 749316.

Chiang, M., Lombardi, D., Du, J., Makrum, U., Sitthichai, R., Harrington, A., Shukair, N., Zhao, M., Fan, X., 2019. Methamphetamine-associated psychosis: Clinical presentation, biological basis, and treatment options. Hum. Psychopharmacol. 34 (5), e271.

Christian G. Voxel-based morphometry (VBM). 2020. http://dbm.neuro.uni-jena.de/cat/ (accessed Jan 30, 2022).

Cropley, V.L., Klauser, P., Lenroot, R.K., Bruggemann, J., Sundram, S., Bousman, C., Pereira, A., Di Biase, M.A., Weickert, T.W., Weickert, C.S., Pantelis, C., Zalesky, A., 2017. Accelerated gray and white matter deterioration with age in schizophrenia. Am. J. Psychiatry 174 (3), 286–295.

Darke, S., Kaye, S., Duflou, J., Lappin, J., 2019. Completed suicide among methamphetamine users: a national study. Suicide Life-threatening Behav. 49 (1), 328–337.

Farnia, V., Farshchian, F., Farshchian, N., Alikhani, M., Sadeghi Bahmani, D., Brand, S., 2020. Comparisons of voxel-based morphometric brain volumes of individuals with methamphetamine-induced psychotic disorder and schizophrenia spectrum disorder and healthy controls. Neuropsychobiology 79 (2), 170–178.

Fassbender, C., Lesh, T.A., Ursu, S., Salo, R., 2015. Reaction time variability and related brain activity in methamphetamine psychosis. Biol. Psychiatry 77 (5), 465–474.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR axis I Disorders, Research Version, patient ed. (SCID-I/P). Biometrics Research, New York State Psychiatric Institute, New York.

Fluyau, D., Mitra, P., Lorthe, K., 2019. Antipsychotics for amphetamine psychosis. A systematic review. *Front. Psychiatry* 10, 740.

NHS Foundation Trust. Guidelines for antipsychotic medication switches. Humber NHS. Approved by HFTDTC: March 2009; Approved by HERPC Nov 2009; Last Reviewed September 2012. https://www.psychdb.com/_media/meds/antipsychotics/nhs_guidelines_antipsychotic_switch.pdf.

Gardoni, F., Bellone, C., 2015. Modulation of the glutamatergic transmission by Dopamine: a focus on Parkinson, Huntington and Addiction diseases. Front. Cell. Neurosci. 9, 25.

Glasner-Edwards, S., Mooney, L.J., 2014. Methamphetamine psychosis: epidemiology and management. CNS Drugs 28 (12), 1115–1126.

Grant, K.M., LeVan, T.D., Wells, S.M., Li, M., Stoltenberg, S.F., Gendelman, H.E., Carlo, G., Bevins, R.A., 2012. Methamphetamine-associated psychosis. J. Neuroimmune Pharmacol. 7 (1), 113–139.

Haijma, S.V., Van Haren, N., Cahn, W., Koolschijn, P.C., Hulshoff Pol, H.E., Kahn, R.S., 2013. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr. Bull. 39 (5), 1129–1138.

Hall, M.G., Alhassoon, O.M., Stern, M.J., Wollman, S.C., Kimmel, C.L., Perez-Figueroa, A., Radua, J., 2015. Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: a neuroimaging meta-analysis. Am. J. Drug Alcohol Abuse 41 (4), 290–299.

Ho, B.C., Andreasen, N.C., Ziebell, S., Pierson, R., Magnotta, V., 2011. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch. Gen. Psychiatry 68 (2), 128–137.

Honea, R., Crow, T.J., Passingham, D., Mackay, C.E., 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am. J. Psychiatry 162 (12), 2233–2245.

Hsieh, J.H., Stein, D.J., Howells, F.M., 2014. The neurobiology of methamphetamine induced psychosis. Front. Hum. Neurosci. 8, 537.

Ipser, J.C., Uhlmann, A., Taylor, P., Harvey, B.H., Wilson, D., Stein, D.J., 2018. Distinct intrinsic functional brain network abnormalities in methamphetamine-dependent patients with and without a history of psychosis. Addict. Biol. 23 (1), 347–358.

Jan, R.K., Kydd, R.R., Russell, B.R., 2012. Functional and structural brain changes associated with methamphetamine abuse. Brain Sci. 2 (4), 434–482.

Jauhar, S., McCutcheon, R., Borgan, F., Veronese, M., Nour, M., Pepper, F., Rogdaki, M., Stone, J., Egerton, A., Turkheimer, F., McGuire, P., Howes, O.D., 2018. The relationship between cortical glutamate and striatal dopamine in first-episode psychosis: a cross-sectional multimodal PET and magnetic resonance spectroscopy imaging study. Lancet Psychiatry 5 (10), 816–823.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Klein, S.D., Shekels, L.L., McGuire, K.A., Sponheim, S.R., 2020. Neural anomalies during vigilance in schizophrenia: Diagnostic specificity and genetic associations. NeuroImage Clin. 28, 102414.

Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Goff, D., West, W.C., Williams, S.C.R., van der Kouwe, A.J.W., Salat, D.H., Dale, A.M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch. Gen. Psychiatry 60 (9), 878.

Liao, Y., Tang, J., Corlett, P.R., Wang, X., Yang, M., Chen, H., Liu, T., Chen, X., Hao, W., Fletcher, P.C., 2011. Reduced dorsal prefrontal gray matter after chronic ketamine use. Biol. Psychiatry 69 (1), 42–48.
London, E.D., Kohno, M., Morales, A.M., Ballard, M.E., 2015. Chronic methamphetamine abuse and corticostriatal deficits revealed by neuroimaging. Brain Res. 1628 (Pt A), 174–185.
Mancuso, L., Fornito, A., Costa, T., Ficco, L., Liloia, D., Manuello, J., Duca, S., Cauda, F., 2020. A meta-analytic approach to mapping co-occurrent grey matter volume increases and decreases in psychiatric disorders. NeuroImage 222, 117220.
McCutcheon, R.A., Krystal, J.H., Howes, O.D., 2020. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. World Psychiatry 19 (1), 15–33.
McKetin, R., Lubman, D.I., Najman, J.M., Dawe, S., Butterworth, P., Baker, A.L., 2014. Does methamphetamine use increase violent behaviour? Evidence from a prospective longitudinal study. Addiction 109 (5), 798–806.
Mubarik, A., Tohid, H., 2016. Frontal lobe alterations in schizophrenia: a review. Trends Psychiatry Psychotherapy 38 (4), 198–206.
Nenadic, I., Sauer, H., Smesny, S., Gaser, C., 2012. Aging effects on regional brain structural changes in schizophrenia. Schizophr. Bull. 38 (4), 838–844.
Nie, L., Zhao, Z., Wen, X., Luo, W., Ju, T., Ren, A., et al., 2020. Gray-matter structure in long-term abstinent methamphetamine users. BMC Psychiatry 20 (1), 158.
Nuechterlein, K.H., Green, M.F., Calkins, M.E., Greenwood, T.A., Gur, R.E., Gur, R.C., Lazzeroni, L.C., Light, G.A., Radant, A.D., Seidman, L.J., Siever, L.J., Silverman, J. M., Sprock, J., Stone, W.S., Sugar, C.A., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Braff, D.L., 2015. Attention/vigilance in schizophrenia: performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS). Schizophr. Res. 163 (1-3), 38–46.
Oka, M., Ito, K., Koga, M., Kusumi, I., 2020. Changes in subunit composition of NMDA receptors in animal models of schizophrenia by repeated administration of methamphetamine. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 103, 109984.
Okada, N., Fukunaga, M., Yamashita, F., Koshiyama, D., Yamamori, H., Ohi, K., Yasuda, Y., Fujimoto, M., Watanabe, Y., Yahata, N., Nemoto, K., Hibar, D.P., van Erp, T.G.M., Fujino, H., Isobe, M., Isomura, S., Natsubori, T., Narita, H., Hashimoto, N., Miyata, J., Koike, S., Takahashi, T., Yamasue, H., Matsuo, K., Onitsuka, T., Iidaka, T., Kawasaki, Y., Yoshimura, R., Watanabe, Y., Suzuki, M., Turner, J.A., Takeda, M., Thompson, P.M., Ozaki, N., Kasai, K., Hashimoto, R., 2016. Abnormal asymmetries in subcortical brain volume in schizophrenia. Mol. Psychiatry 21 (10), 1460–1466.
Okada, N., Takahashi, K., Nishimura, Y., Koike, S., Ishii-Takahashi, A., Sakakibara, E., Satomura, Y., Kinoshita, A., Takizawa, R., Kawasaki, S., Nakakita, M., Ohtani, T., Okazaki, Y., Kasai, K., 2016. Characterizing prefrontal cortical activity during inhibition task in methamphetamine-associated psychosis versus schizophrenia: a multi-channel near-infrared spectroscopy study. Addict. Biol. 21 (2), 489–503.
Pando-Naude, V., Toxto, S., Fernandez-Lozano, S., Parsons, C.E., Alcauter, S., Garza-Villarreal, E.A., 2021. Gray and white matter morphology in substance use disorders: a neuroimaging systematic review and meta-analysis. Transl. Psychiatry 11 (1), 29.
Mikhail Pletnikov, John Waddington. Modeling the Psychopathological Dimensions of Schizophrenia From Molecules to Behavior. 2015. Retrieved from https://www.skoltech.ru/app/data/uploads/sites/2/2016/04/SCH-book-Pletnikov-and-Waddington-2016-GSK3-chapter.pdf.
Ruan, X., Zhong, N., Yang, Z., Fan, X., Zhuang, W., Du, J., et al., 2018. Gray matter volume showed dynamic alterations in methamphetamine users at 6 and 12months abstinence: A longitudinal voxel-based morphometry study. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 81, 350–355.
Sani, I., Stemmann, H., Caron, B., Bullock, D., Stemmler, T., Fahle, M., Pestilli, F., Freiwald, W.A., 2021. The human endogenous attentional control network includes a ventro-temporal cortical node. Nat. Commun. 12 (1).
Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophr. Res. 49 (1–2), 1–52.
Swanson, J.M., Wigal, T.L., Volkow, N.D., 2011. Contrast of medical and nonmedical use of stimulant drugs, basis for the distinction, and risk of addiction: comment on Smith and Farah (2011). Psychol. Bull. 137 (5), 742–748.
Tost, H., Alam, T., Meyer-Lindenberg, A., 2010. Dopamine and psychosis: theory, pathomechanisms and intermediate phenotypes. Neurosci. Biobehav. Rev. 34 (5), 689–700.
Uhlmann, A., Fouche, J.P., Koen, N., Meintjes, E.M., Wilson, D., Stein, D.J., 2016. Fronto-temporal alterations and affect regulation in methamphetamine dependence with and without a history of psychosis. Psychiatry Res. Neuroimaging 248, 30–38.
Uhlmann, A., Fouche, J.P., Lederer, K., Meintjes, E.M., Wilson, D., Stein, D.J., 2016. White matter microstructure and impulsivity in methamphetamine dependence with and without a history of psychosis. Hum. Brain Mapp. 37 (6), 2055–2067.
van Erp, T.G.M., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., Agartz, I., Westlye, L.T., Haukvik, U.K., Dale, A.M., Melle, I., Hartberg, C.B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D.W., Cannon, D.M., Corvin, A., Machielsen, M.W.J., Koenders, L., de Haan, L., Veltman, D.J., Satterthwaite, T.D., Wolf, D.H., Gur, R.C., Gur, R.E., Potkin, S.G., Mathalon, D.H., Mueller, B.A., Preda, A., Macciardi, F., Ehrlich, S., Walton, E., Hass, J., Calhoun, V.D., Bockholt, H.J., Sponheim, S.R., Shoemaker, J.M., van Haren, N.E.M., Pol, H.E.H., Ophoff, R.A., Kahn, R.S., Roiz-Santiañez, R., Crespo-Facorro, B., Wang, L., Alpert, K.I., Jönsson, E.G., Dimitrova, R., Bois, C., Whalley, H.C., McIntosh, A.M., Lawrie, S.M., Hashimoto, R., Thompson, P. M., Turner, J.A., 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol. Psychiatry 21 (4), 547–553.
Veijola J, Guo JY, Moilanen JS, Jaaskelainen E, Miettunen J, Kyllonen M *et al.* Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. *PloS one* 2014; 9(7): e101689.
Voce, A., Calabria, B., Burns, R., Castle, D., McKetin, R., 2019. A systematic review of the symptom profile and course of methamphetamine-associated psychosissubstance use and misuse. Subst. Use Misuse 54 (4), 549–559.
Wikipedia, the free encyclopedia. Vigilance (psychology).15 Jun, 2021. https://en.wikipedia.org/wiki/Vigilance_(psychology). (accessed Feb 15, 2022).
Winship, I.R., Dursun, S.M., Baker, G.B., Balista, P.A., Kandratavicius, L., Maia-de-Oliveira, J.P., Hallak, J., Howland, J.G., 2019. An Overview of Animal Models Related to Schizophrenia. Canadian journal of psychiatry Revue canadienne de psychiatrie 64 (1), 5–17.
World Medical Association. Declaration of Helsinki 2008. https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2008.pdf (accessed Sept 30, 2022).
Yamamuro, K., Makinodan, M., Kimoto, S., Kishimoto, N., Morimoto, T., Toritsuka, M., Matsuoka, K., Takebayashi, Y., Takata, T., Takahashi, M., Tanimura, Y., Nishihata, Y., Matsuda, Y., Ota, T., Yoshino, H., Iida, J., Kishimoto, T., 2015. Differential patterns of blood oxygenation in the prefrontal cortex between patients with methamphetamine-induced psychosis and schizophrenia. Sci. Rep. 5 (1).
Yang, M., Jia, X., Zhou, H., Ren, P., Deng, H., Kong, Z., Xie, C., Hu, W., Jiang, W., Lai, W., Zhang, B., Zhao, M., Liu, T., 2021. Brain dysfunction of methamphetamine-associated psychosis in resting state: Approaching schizophrenia and critical role of right superior temporal deficit. Addict. Biol. 26 (6), e13044.
Yang, C., Tang, J., Liu, N., Yao, L.i., Xu, M., Sun, H., Tao, B.o., Gong, Q., Cao, H., Zhang, W., Lui, S.u., 2021. The effects of antipsychotic treatment on the brain of patients with first-episode schizophrenia: a selective review of longitudinal MRI studies. Front. Psychiatry 12, 593703.
Yang, M., Yang, C., Liu, T., London, E.D., 2020. Methamphetamine-associated psychosis: links to drug use characteristics and similarity to primary psychosis. Int. J. Psychiatry Clin. Practice 24 (1), 31–37.
Zhang, S., Hu, Q., Tang, T., Liu, C., Li, C., Zang, Y.-Y., Cai, W.-X., 2018. Changes in gray matter density, regional homogeneity, and functional connectivity in methamphetamine-associated psychosis: a resting-state functional magnetic resonance imaging (fMRI) study. Med. Sci. Monitor 24, 4020–4030.
Zhong, N., Zhao, M., 2019. Computerized cognitive tests of Cogstate and the applicability. Psychol. Commun. 1, 67–70.