Subcortical volumes, frontal cortical thickness, and pro-inflammatory cytokines in schizophrenia versus methamphetamine-induced psychosis

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Abstract

Background: Clinical features of schizophrenia and methamphetamine-induced psychosis (MAP) have significant overlap. Schizophrenia is associated with alterations in subcortical volumes, cortical thickness and pro-inflammatory cytokines that may correlate with clinical features. However, analogous work on MAP is lacking. This study compared subcortical volumes, cortical thickness and pro-inflammatory cytokines in individuals with schizophrenia, MAP, and healthy controls. It also assessed associations of neuroimaging measures and cytokine levels with each other, with illness duration and symptom severity in schizophrenia and MAP, and with duration of substance use in MAP.

Methods: Participants included 36 individuals with schizophrenia, 27 with MAP, and 32 healthy controls matched for age and sex. Diagnosis was determined using the Structured Clinical Interview for Axis I Disorders and symptom severity was assessed using the Positive and Negative Syndrome Scale. Structural T1-weighted images were acquired using a 3 Tesla magnetic resonance imaging scanner. Serum peripheral cytokine concentrations levels were measured using a multiplex bead array. Analysis of covariance was used to compare measures across groups.

Results: Individuals with schizophrenia and with MAP had decreased left amygdala volumes and frontal cortical thickness compared to healthy controls. Individuals with schizophrenia had increased volumes in bilateral caudate, putamen, and nucleus accumbens compared to healthy controls, and increased right globus pallidus and NAcc volumes compared to MAP. Individuals with MAP had increased right orbitofrontal cortical thickness compared to healthy controls. Decreased left amygdala volumes and frontal cortical thickness were significantly associated with longer illness duration in schizophrenia, and with longer duration of methamphetamine use in MAP. There was no significant difference across groups in cytokine levels, and no significant associations of cytokine levels with neuroimaging or clinical measures.

Conclusion: This study found overlaps and differences in the neurobiology of schizophrenia and MAP, a finding that is consistent with previous research. Further studies with larger sample sizes and more robust measures are needed to understand immune mechanisms underlying these conditions.

Keywords: Schizophrenia; Methamphetamine-induced psychosis; Amygdala; Basal ganglia; Inflammation; Magnetic Resonance Imaging

1. Introduction

There is considerable overlap in the clinical features of schizophrenia and methamphetamine-induced psychosis (MAP). Both schizophrenia and MAP are, for example, characterized by positive symptoms of psychosis. Furthermore they may share aspects of neurobiology, with positive symptoms in both conditions responding to treatment with dopamine blockers. Thus, it has been suggested that MAP may serve as an important model for understanding the neurobiology of schizophrenia. Nevertheless, few studies have directly compared the neuroimaging signatures of schizophrenia and MAP.

Structural magnetic resonance imaging (MRI) studies have shown differences in subcortical gray matter volumes in schizophrenia, and these have been associated with clinical symptom profiles (Duan et al., 2021; Fan et al., 2019; Koshiyama et al., 2018; Makowski et al., 2017; Rajarethinam et al., 2001). In schizophrenia, for example, decreased hippocampal volume has been associated with negative symptoms and hallucinations (Duan et al., 2021; Rajarethinam et al., 2001), and decreased amygdala-hippocampal complex associated with negative symptoms of psychosis (Rajarethinam et al., 2001). Furthermore, increased basal ganglia volumes have been consistently observed in schizophrenia compared to healthy controls (Chakos et al., 1994; Corson et al., 1999; Lauer et al., 2001), with alterations in basal ganglia volumes again associated with both positive and negative symptoms (Duan et al., 2021; Fan et al., 2019; Koshiyama et al., 2018; Makowski et al., 2017; Rajarethinam et al., 2001; Li et al., 2018). Decreased cortical thickness of the frontal and temporal lobes has also been observed in schizophrenia (Kuperberg et al., 2003; Nenadic et al., 2015; Rimol et al., 2010; Rimol et al., 2012; Sugihara et al., 2017; van Erp et al., 2018), with the frontal cortex most affected (van Erp et al., 2018).

While structural neuroimaging studies of MAP are limited, there is some evidence of decreased hippocampal and amygdala volumes in MAP compared to healthy controls (Orikabe et al., 2011), and of increased cortical thickness in MAP compared to methamphetamine dependence (Uhlmann et al., 2016). There are few studies of the association of neuroimaging and clinical measures in MAP. Furthermore, no studies have directly compared subcortical volumes and cortical thickness in schizophrenia versus MAP.

Schizophrenia is further characterized by alterations in immune biomarkers (Prestwood et al., 2021). Notably, alterations of peripheral blood inflammatory cytokines (e.g. TNF)-α, IL-1β, IL-6, IL-8, IL-10, IL-12, and IFN-γ) have been associated with clinical outcomes in this condition (Kose et al., 2021; Pillinger

et al., 2019). However, few studies have investigated immune markers in MAP, and none have directly compared immune markers in schizophrenia to those in MAP. Given findings of associations between neuroimaging measures and cytokine levels in schizophrenia (Wu et al., 2019), and evidence of neuro-inflammation in laboratory models of MA use (Davidson et al., 2022; Shi et al., 2022), it may be informative to investigate associations between neuroimaging measures and cytokines in MAP.

This study aims to compare subcortical volumes, cortical thickness, and cytokine levels in individuals with schizophrenia, MAP, and healthy controls. We also assessed associations of neuroimaging measures and cytokine levels with each other, with illness duration and symptom severity in schizophrenia, and with duration of methamphetamine use and symptoms severity in MAP.

2. Materials and methods

2.1. Participants

Participants between the ages of 20-40 years were recruited from Valkenberg Hospital and Groote Schuur Hospital in Cape Town, and included 36 individuals with schizophrenia, and 27 participants with MAP. 32 healthy controls matched for age and sex, were recruited from the general population in Cape Town.

Individuals with schizophrenia and MAP had clinical diagnosis confirmed with the Structured Clinical Interview for DSM-IV (SCID-I), and symptom severity measured with the Positive and Negative Syndrome Scale (PANSS) (Thompson et al., 2004). The SCID-I was also given to healthy controls so as to include only those without Axis-I disorders. Participants were excluded if they had a history of 1) chronic medical illness that required medical care or prescription medication, including severe brain trauma and intellectual disability; 2) were recently or currently pregnant or lactating; 3) were unable to undergo MRI because of metal implants, claustrophobia, or other reasons; 4) substance dependence other than nicotine dependence. All individuals with MAP had discontinued methamphetamine use.

The work adhered to human research guidelines as stipulated in the Declaration of Helsinki (World Medical, 2013). The protocol underwent ethical review and approval with the University of Cape Town's Human Research Ethics Committee (UCT HSF HREC: 413/2016).

2.2. Imaging procedures

Structural magnetic resonance imaging (sMRI) was conducted at the Cape Universities Body Imaging Centre (CUBIC), using a 3T Siemens Skyra MRI scanner (Siemens Medical Systems, Erlangen, Germany). A 32-channel head coil was used. A high resolution, T1-weighted scans were acquired with a multi-echo MPRAGE structural scan with the following scan parameters: TR= 2530ms; graded TE= 1.69, 3.55, 5.41 and 7.27ms; flip angle= 7°; field of view (FOV)= 256mm; voxel size = 1x1x1mm; 6:39min.

2.3. Image processing

Processing of all MRIs was performed using FreeSurfer v6.0 (Fischl, 2012; Incorporated, 1999) (http://surfer.nmr.mgh.harvard.edu/) using the Desikan-Killiany atlas, for cortical reconstruction and volume segmentation (Desikan et al., 2006). The processing pipeline included motion correction, skull-stripping, Talairach transformation, segmentation of subcortical white matter and deep grey matter volumetric structures, intensity normalization, tessellation of the grey matter/white matter boundary, automated topology correction, and surface deformation and registration to the Desikan-Killiany atlas (Desikan et al., 2006). Reconstruction of the grey and white matter boundary and pial surface was performed to extract cortical thickness measurements (Fischl and Dale, 2000; Fischl et al., 2001; Segonne et al., 2007). Data and statistical summaries were generated using ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols) and RStudio v 1.2.5054 (RStudio Incorporated, 2009-2020).

2.4. Inflammatory markers

Blood samples from all study participants were collected via venepuncture into serum tubes. The tubes were kept at room temperature at for approximately 30 minutes to allow clotting and were subsequently centrifuged at 1,800 × g for 10 min. The separated serum was then aliquoted into cryovials and stored at -80 °C until analyses. The Luminex Milliplex® MAP human cytokine / chemokine magnetic bead panel (HSTCMAG28SK07; Merck) was used to detect cytokines; TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-12p, and IFN-γ. The intra-assay coefficients of variation for each cytokine were all below 14%. All plates were analysed on the same day. Serum measures for IL-6 were below the detectable limit and were consequently excluded from statistical analysis.

2.5. Statistical analyses

To compare brain measures across schizophrenia, MAP, and healthy controls, we employed multiple analysis of covariance (MANCOVA) for parametric data and Kruskal Wallis analysis of covariance (ANCOVA) for non-parametric data ($p < 0.05$), with intracranial volume (ICV) (Mathalon et al., 1993; O'Brien et al., 2011; Sanfilipo et al., 2004), sex, and age (Barnes et al., 2010; Crowley et al., 2018; Smith et al., 2007) as covariates for subcortical volume measurements and, sex and age as covariates for cortical thickness measurements. Spearman's Rank correlations (for non-normally distributed data) and Pearson's correlations (for normally distributed data) were performed within each group to determine associations of neuroimaging measures and cytokine levels with illness duration and symptom severity in schizophrenia, and with duration of methamphetamine use and symptom severity in MAP. Significance levels were set at Rho of ± 0.5 and $p < 0.01$ (where the critical value for r = 0.449 when $p = 0.01$) to reduce Type I Error.

3. Results

3.1. Demographic and clinical variables

There were no significant group differences for age and sex, but lower levels of school education were found in schizophrenia ($H_{(2,94)} = 19.8$, $p = 0.002$) and in MAP ($H_{(2,94)} = 19.8$, $p = 0.00046$), compared to healthy controls (Table 1). Duration of illness was significantly longer in schizophrenia than in MAP ($z = 3.2$, $p = 0.0008$). Both participants with schizophrenia and MAP had increased scores on the PANSS positive, negative, general and total scores compared to healthy controls.

Table 1: Demographics, duration of illness, and symptom severity in schizophrenia, methamphetamine-induced psychosis, and health controls

	CONTROLS (n = 32) 13 females: 19 males			**SCHIZOPHRENIA (n = 36)** 8 females: 28 males			**MAP (n = 27)** 6 females: 21 males				
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Test statistics	Group differences
Age on day of study	30.12	4.8	23 -– 40	29.53	5.36	22 -– 39	27.89	4.74	20 – 37	$H_{(2,94)}$= 3.09, p = 0.21	
School education (years)	11.65	0.91	9 – 13[a]	10.11	1.94	4 -– 12	9.56	2.55	1 -– 12	$H_{(2,94)}$= 19.83, p < 0.01	CON vs. schizophrenia, p < 0.01; CON vs. MAP, p < 0.01
Post-school education (years)	0.94	1.35	0 – 4	0.25	0.88	0 – 5	0.61	1.14	0 -– 4	$H_{(2,94)}$= 8.44, p = 0.02	n.s.
Total education duration (years)	12.58	1.85	9 – 16[b]	10.37	2.28	4 -– 17	10.17	3.16	1 -– 16	$H_{(2,94)}$= 18.829, p < 0.01	CON vs. schizophrenia, p < 0.01; CON vs. MAP, p < 0.01
Duration of illness (months)	-	-	-	102.31	52.61	14 – 228[c]	60	48.34	2 – 180	U =250, z = 3.271, p < 0.01	
Antipsychotic use variables											
Chlorpromazine equivalents	-	-	-	337.72	289.02	0-1100	210.74	198.76	0 -750		
Methamphetamine use measures											
Duration of use (months)	-	-	-	64.80	46.16	24-144	104.56	51.64	24 – 228		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range		
Abstinence (months)	-	-	-	40.41	46.793	0.03 – 132	8.01	13.47	0.03 – 48		
Psychotic symptomatology PANSS											
Positive scale	7.10	0.41	7 – 9	12.16	4.88	7 – 25[d]	10.59	5.23	1 – 23	$H_{(2,92)}$= 40.21, p < 0.01	CON vs. schizophrenia, p < 0.01; CON vs. MAP, p < 0.01
Negative scale	7.07	0.26	7 – 8	14.89	6.41	7– 28[d]	14.30	10.02	7 – 45	$H_{(2,92)}$= 43.86, p < 0.01	CON vs. schizophrenia, p < 0.01; CON vs. MAP, p < 0.01
General psychopathology	16.31	0.71	16 – 19	21.81	7.08	16 – 45[d]	20.74	6.21	16 – 37	$H_{(2,92)}$= 32.99, p < 0.01	CON vs. schizophrenia, p < 0.01; CON vs. MAP, p < 0.01
Total score	30.48	1.12	30 -35	48.86	15.56	30 – 91[e]	45.63	18.68	30 – 97	$H_{(2,92)}$= 46.64, p < 0.01	CON vs. schizophrenia, p < 0.01; CON vs. MAP, p < 0.01

[a] CON longer duration of school education compared to schizophrenia and MAP
[b] CON longer duration total education than schizophrenia and MAP
[c] schizophrenia greater duration of illness compared to MAP
[d] schizophrenia higher scores than CON and MAP
[e] schizophrenia lower scores than MAP
Groups: CON – healthy controls; MAP – methamphetamine-induced psychosis. PANSS – Positive and Negative Syndrome Scale; SD – standard deviation.

3.2 Subcortical volumes

There were decreased left amygdala volumes in schizophrenia ($F_{(2,88)}$ = 6.37, p = 0.01) and in MAP ($F_{(2,88)}$ = 6.37, p = 0.005) compared to healthy controls. There was a trend towards a significant group difference in right hippocampal volumes ($F_{(2,88)}$ = 2.48, p = 0.089). There were increased bilateral caudate ($F_{(6,178)}$ = 4.11, p = 0.03; $F_{(6,178)}$ = 3.95, p = 0.05), putamen ($F_{(6,178)}$ = 6.85, p = 0.016; $F_{(6,178)}$ = 5.27, p = 0.0072) and NAcc ($F_{(6,178)}$ = 18.69, p < 0.0001; $F_{(6,178)}$ = 7.83, p < 0.014) volumes in schizophrenia compared to healthy controls. There were increased right globus pallidus ($F_{(6,178)}$ = 3.81, p = 0.021) and bilateral NAcc ($F_{(6,178)}$ = 18.69; p < 0.0001; $F_{(6,178)}$ = 7.83, p = 0.0017) volumes in schizophrenia compared to MAP.

3.3 Frontal cortical thickness

There was decreased frontal cortical thickness in schizophrenia compared to healthy controls (Table 2) in the left caudal middle frontal ($F_{(4,180)}$ = 36.2, p < 0.0001), right caudal middle frontal ($F_{(4,180)}$ = 17.9, p < 0.0001), left lateral orbitofrontal ($H_{(2,94)}$ = 60.76, p < 0.0001), left rostral middle frontal ($F_{(4,180)}$ = 40.0, p < 0.0001), left frontal pole ($H_{(2,94)}$ = 82.30, p < 0.0001), right frontal pole ($H_{(2,94)}$ = 64.36, p < 0.0001), left pars opercularis ($F_{(4,180)}$ = 82.5, p < 0.0001), right pars opercularis ($F_{(4,180)}$ = 31.6, p < 0.0001), left pars orbitalis ($F_{(4,180)}$ = 10.5, p = 0.0001), right pars orbitalis ($F_{(4,180)}$ = 13.9, p = 0.0001) and right ($H_{(2,94)}$ = 30.18, p = 0.00035) and left pars triangularis ($F_{(4,180)}$ = 29.2, p < 0.0001). There was also decreased frontal cortical thickness in MAP compared to healthy controls for the left caudal middle frontal ($F_{(4,180)}$ = 36.2, p < 0.0001), right caudal middle frontal ($F_{(4,180)}$ = 17.9, p = 0.0001), left rostral middle frontal ($F_{(4,180)}$ = 40.0, p < 0.0001), left superior frontal ($F_{(4,180)}$ = 10.5, p = 0.013), left pars opercularis ($F_{(4,180)}$ = 82.5, p < 0.0001), right pars opercularis ($F_{(4,180)}$ = 31.6, p < 0.0001), left pars orbitalis ($F_{(4,180)}$ = 10.5, p = 0.0068), right pars orbitalis ($F_{(4,180)}$ = 13.9, p = 0.0002), left frontal pole ($H_{(2,94)}$ = 82.30, p < 0.0001) and right frontal pole ($H_{(2,94)}$ = 64.36, p < 0.0001). There was increased cortical thickness in MAP compared to healthy controls in right medial orbitofrontal ($H_{(2,94)}$ = 7.21, p = 0.042) and right lateral orbitofrontal ($F_{(4,180)}$ = 10.7, p = 0.028) cortex. There was increased frontal cortical thickness in MAP compared to schizophrenia for the right lateral orbitofrontal ($F_{(4,180)}$ = 10.7, p < 0.0001), left pars opercularis ($F_{(4,180)}$ = 82.5, p < 0.0001), left pars triangularis ($F_{(4,180)}$ = 29.2, p < 0.0001), left lateral orbitofrontal ($H_{(2,94)}$ = 60.76, p < 0.0001), left medial orbitofrontal ($H_{(2,94)}$ = 12.22, p = 0.0014), left frontal pole ($H_{(2,94)}$ = 82.30, p < 0.0001) and right pars triangularis ($F_{(4,180)}$ = 29.2, p < 0.0001). There was

increased frontal cortical thickness in schizophrenia compared to MAP for the right rostral middle frontal ($H_{(2,94)}$ = 10.78, p = 0.0032) and the right pars opercularis ($F_{(4,180)}$ = 31.6, p = 0.0001).

Table 2: Frontal cortical thickness group differences

Regions	Effect size	SCZ-CON	MAP-CON	MAP-SCZ
		p	*p*	*p*
Left caudal middle frontal*	36.2	< 0.0001	< 0.0001	n.s.
Right caudal middle frontal*	19.9	< 0.0001	< 0.0001	n.s.
Left lateral orbitofrontal#	60.76	< 0.0001	n.s.	< 0.0001
Right lateral orbitofrontal*	10.7	n.s.	0.028	< 0.0001
Left medial orbitofrontal#	12.22	n.s.	n.s.	0.0014
Right medial orbitofrontal#	7.21	n.s.	0.042	n.s.
Left rostral middle frontal*	40	<0.0001	< 0.0001	n.s.
Right rostral middle frontal#	10.78	n.s.	n.s.	0.0032
Left superior frontal*	10.5	< 0.0001	0.013	n.s.
Right superior frontal*	4.3	0.015	n.s.	n.s.
Left frontal pole#	82.3	< 0.0001	0.0002	< 0.0001
Right frontal pole#	64.36	< 0.0001	< 0.0001	n.s.
Left pars opercularis*	82.5	< 0.0001	< 0.0001	< 0.0001
Right pars opercularis*	31.6	< 0.0001	< 0.0001	0.0001
Left pars orbitalis*	10.5	< 0.0001	0.0068	n.s.
Right pars orbitalis*	13.9	< 0.0001	0.0002	n.s.
Left pars triangularis*	29.2	< 0.0001	n.s.	< 0.0001
Right pars triangularis	30.18	0.0004	n.s.	< 0.0001

Effect size: for all group differences. *MANOVA ($F_{(4,180)}$) and #Kruskal Wallis ANOVA ($H_{(2,94)}$) were performed for frontal cortical thickness in methamphetamine-induced psychosis (MAP), schizophrenia (SCZ) and healthy controls (CON) groups, with *p*-values of <0.05 considered statistically significant. N.s : results which did not survive the MANOVA and Kruskal Wallis ANOVA.

3.4 Cytokines

There were no significant group differences in cytokine concentrations for IFN-γ ($H_{2,94}$ = 2.81; p = 0.245), IL-10 ($H_{2,94}$ = 0.93, p = 0.627), IL-12 ($H_{2,94}$ = 4.90, p = 0.0862), IL-1β ($H_{2,94}$ = 1.27, p = 0.531), IL-8 ($H_{2,94}$ = 0.23; p =0.892) and TNF-α ($H_{2,94}$ = 1.01, p = 0.605).

3.5 Associations of neuroimaging measures and pro-inflammatory cytokines

There were no significant associations between neuroimaging measures, cytokine levels, and symptom severity.

In schizophrenia, increased illness duration was associated with left amygdala volumes ($R_{(n=36)}$ = -0.43, p = 0.009), and decreased cortical thickness ($R_{(n=36)}$ < - 0.51, p < 0.001), except for the left frontal pole ($R_{(n=36)}$ = + 0.48, p = 0.0029) and right frontal pole ($R_{(n=36)}$= + 0.37, p = 0.025). In particular, increased illness duration was associated with decreased cortical thickness of the right caudal middle frontal ($R_{(n=36)}$ = -0.63, p < 0.0001), left caudal middle frontal ($R_{(n=36)}$ = -0.64, p < 0.0001), left lateral orbitofrontal ($R_{(n=36)}$ = -0.512, p = 0.0013), right lateral orbitofrontal ($R_{(n=36)}$ = -0.62, p < 0.0001), left medial orbitofrontal ($R_{(n=36)}$ = -0.58, p = 0.00020), right medial orbitofrontal ($R_{(n=36)}$ = -0.55, p = 0.00050), left rostral middle frontal ($R_{(n=36)}$ = -0.60, p = 0.00011), right rostral middle frontal ($R_{(n=36)}$ = -0.57, p = 0.00029), left superior frontal ($R_{(n=36)}$ = -0.59, p = 0.00014), right superior frontal ($R_{(n=36)}$ = -0.63; p < 0.0001), left pars opercularis ($R_{(n=36)}$ = -0.65, p < 0.0001), right pars opercularis ($R_{(n=36)}$ = -0.63, p < 0.0001), left pars orbitalis ($R_{(n=36)}$ = -0.64, p < 0.0001), right pars orbitalis ($R_{(n=36)}$ = -0.650, p < 0.0001), left pars triangularis ($R_{(n=36)}$ = -0.58, p = 0.0002) and the right pars triangularis ($R_{(n=36)}$ = -0.65, p < 0.0001).

In MAP, increased duration of methamphetamine use was associated with decreased left amygdala ($r_{(n=27)}$ = -0.51, p = 0.007) volumes, left lateral orbitofrontal ($R_{(n=27)}$ = -0.54, p = 0.003), left medial orbitofrontal ($R_{(n=27)}$ = -0.55; p = 0.003), right medial orbitofrontal ($R_{(n=27)}$ = -0.55, p = 0.003), right rostral middle frontal ($R_{(n=27)}$ = -0.55, p = 0.003) and left frontal pole ($R_{(n=27)}$ = -0.55, p = 0.003).

4. Discussion

Several key findings emerged in this study. Individuals with schizophrenia and with MAP had decreased left amygdala volumes and frontal cortical thickness compared to healthy controls. Individuals with schizophrenia had increased volumes in bilateral caudate, putamen, and nucleus accumbens compared to healthy controls, and increased right globus pallidus and Nacc volumes compared to MAP. Individuals with MAP had increased right orbitofrontal cortical thickness compared to healthy controls. Decreased left amygdala volumes and frontal cortical thickness were significantly associated with longer illness duration in schizophrenia, and with longer duration of methamphetamine use in MAP. There was no significant difference across groups in cytokine levels, and no significant associations of cytokine levels with neuroimaging or clinical measures.

Our findings with respect to amygdala volumes and frontal cortical thickness are consistent with previous work indicating that decreased left amygdala volumes and frontal cortical thinning are present in both schizophrenia (Niu et al., 2004; van Erp et al., 2016) and MAP (Orikabe et al., 2011; Uhlmann et al., 2016) compared to healthy controls, and are associated with duration of illness in schizophrenia (Bustillo et al., 2001; Molina et al., 2011). This study is the first, to our knowledge, to show that decreased left amygdala volumes and frontal cortical thickness are significantly associated with longer duration of methamphetamine use in MAP. Taken together, these findings suggest important overlaps in the neurobiology of schizophrenia and MAP. Decreased cortical thickness may reflect decreased neural density and functional dysconnectivity to subcortical and other cortical brain regions, in both schizophrenia (Lewis et al., 2012; Li et al., 2019; Li et al., 2016) and MAP.

Our findings of increased caudate volume in schizophrenia but not in MAP, is consistent with previous work on schizophrenia, where it has been attributed to typical antipsychotic use (Breier et al., 1992; Chakos et al., 1994; Emsley et al., 2023; Jørgensen et al., 2016; Lang et al., 2004). Similarly, increased basal ganglia volumes has been found in several studies of schizophrenia (Emsley et al., 2023; Hokama et al., 1995; Kitabayashi et al., 2006; Mamah et al., 2007; van Erp et al., 2016). The finding that globus pallidus and NAcc volume were increased in schizophrenia compared with MAP, but that right orbitofrontal cortex thickness is decreased in schizophrenia compared with MAP are novel ones, and point to important differences in the neurobiology of these conditions. However, it is also possible,

however, that such findings point to differences in the extent of antipsychotic use in schizophrenia vs MAP.

We found no significant differences in cytokine concentrations across groups. Furthermore, no significant associations were observed between neuroimaging measures and cytokines levels. There is some inconsistency in the literature on immune markers on schizophrenia; our findings are consistent with some previous work (Kaminska et al., 2001; Lv et al., 2015; Miller et al., 2011; Potvin et al., 2008; Wilke et al., 1996). However, we cannot rule out the possibility that our negative findings are due to insufficient power. Moreover, the anti-inflammatory effects of antipsychotic medication in both schizophrenia and MAP groups may have ameliorated the inflammatory status in these study groups (Flatow et al., 2013; Fraguas et al., 2019; Miller et al., 2011).

A number of limitations deserve emphasis. First, as alluded to above, the use of antipsychotics in both schizophrenia and MAP may have confounded the findings reported in this study. Second, although our sample size is consistent with previous work on MAP, the small sample size warrants replication in a larger study. Third, self-reported MA abstinence was not supported by an objective confirmation.

4.1.1 Conclusion

In summary our findings suggest both overlaps and differences in the neurobiology of schizophrenia and MAP, a conclusion that is consistent with previous work. Larger samples and more robust measures are needed to fully delineate overlap and differences in immune mechanisms across these two conditions.

Role in study L.B. recruitment, neuroimaging analysis, cytokine analysis, statistical analysis and writing. K.C.W. recruitment, cytokine analysis and writing assistance. H.T. clinician, A.A.U, neuroimaging and writing assistance, A.B. recruitment. D.J.S. writing assistance and P.N. cytokine analysis and writing assistance.

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