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Higher blood–brain barrier leakage in schizophrenia-spectrum disorders: A comparative dynamic contrast-enhanced magnetic resonance imaging study with healthy controls

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ABSTRACT

Background: Blood-brain barrier (BBB) disruptions are presumed to be implicated in schizophrenia-spectrum disorders (SSDs). Previous studies focused on cerebrospinal fluid (CSF) markers, which are imprecise for detecting subtle BBB disruption. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) enables sensitive investigation of subtle BBB leakage in vivo, yet remains unexplored in SSD research. We hypothesized higher leakage in SSDs compared to healthy controls (HCs), indicating a clinical sub-phenotype.

Methods: Forty-one people with SSDs and forty age- and sex-matched HCs were included in this cross-sectional study employing DCE-MRI, clinical characterization, cognitive assessment, blood and CSF analyses. The volume transfer constant K_{trans}, calculated using the Patlak method to estimate the contrast agent transfer between blood and extravascular space, was compared between groups to detect differences in BBB leakage.

Results: Individuals with SSDs showed higher BBB leakage compared to HCs in a widespread pattern, in brain regions typically affected in SSDs. No significant association was detected between leakage and measures of cognition, symptom severity, peripheral inflammation markers and albumin CSF/serum ratio.

Conclusions: This is the first study to date reporting BBB leakage in SSDs compared to HCs in multiple brain regions implicated in the disorder. These findings provide insights into disease mechanisms, highlighting the need for further investigation into the role of the BBB in SSDs.

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1. Introduction

Despite advances in etiological research, the precise biological underpinnings underlying schizophrenia-spectrum disorders (SSDs) remain elusive. As a crucial interface between the periphery and the brain, the blood–brain barrier (BBB) has gained increasing research attention (Pollak et al., 2018). BBB breakdown and associated inflammation are speculated to initiate the early stages in the pathological cascade leading to neurodegeneration in neuropsychiatric disorders (Montagne et al., 2015; van de Haar et al., 2016) and BBB breakdown has been proposed as an early biomarker for cognitive dysfunction (Barisano et al., 2022; Nation et al., 2019).

Evidence of BBB alterations stems from postmortem studies, serum and cerebrospinal fluid biomarker analyses, and advanced neuroimaging research. In SSDs, postmortem studies have revealed structural and morphological abnormalities, alterations in molecular marker expression, gene expression patterns, and immunological abnormalities (Zhang et al., 2025). Structural abnormalities included differences in capillaries and NVU (neurovascular unit) cell types, i.e. reduced number of pericapillary oligodendrocytes (Vostrikov et al., 2008) and decreased quantity of glial fibrillary acidic protein (GFAP)-positive astrocytes surrounding blood vessels (Webster et al., 2001), along with endothelial cell vacuolation, astrocytic end-foot thickening, and basal membrane thickening (Uranova et al., 2010). Immunological abnormalities included infiltration of CD3 + T lymphocytes and CD20 + B lymphocytes (Busse et al., 2012) as well as elevated IgG levels in the temporal cortex in hippocampal areas in SSD brains, suggesting inflammatory BBB leakage. However, postmortem studies are limited by factors such as small sample sizes, variability in cause of death, and the inability to assess dynamic BBB changes in living patients.

In vivo evidence on BBB disruption has been postulated to stem from blood and cerebrospinal fluid (CSF) markers. A study combining magnetic resonance imaging (MRI) of the brain and differential blood analyses observed significantly increased neutrophil granulocytes in first-episode psychosis (FEP) patients (n = 137) vs. controls (n = 81) (Núñez et al., 2019). Neutrophil granulocytes were associated with reduced total brain gray matter and worse psychopathology (Núñez et al., 2019). This was interpreted as neutrophil-associated brain tissue loss in initial stages of SSDs, leading to potential cognitive and clinical decline, based on the hypothesis of BBB dysfunction in SSDs, facilitating cell migration into the brain along with the described destructive neutrophil properties on brain tissue in neurodegenerative diseases (Gadani et al., 2015). Other blood-derived markers proposed to suggest BBB disruption include S100 Calcium Binding Protein B (S100B), expressed in astrocytes and oligodendrocytes (Schümberg et al., 2016) and the BBB-associated proteins like the matrix metallopeptidase 9 (Schoretsanitis et al., 2021). The current state-of-the-art method for evaluating the integrity of the BBB by the ratio of albumin in cerebrospinal fluid (CSF) and blood Albumin ratio (Q_{Alb}) (Pollak et al., 2018).

These fluid blood and CSF biomarkers present notable limitations, including lack of specificity, extracerebral expression (Steiner et al., 2011) (S100B) and susceptibility to be influenced by confounding factors beyond BBB breakdown (Pollak et al., 2018). Moreover, lumbar puncture-derived markers, like Q_{Alb}, primarily allow for the evaluation of the blood-cerebrospinal fluid barrier (BCSFB) rather than the BBB itself (Yakimov et al., 2023).

The prevalence of BCSFB breakdown in SSDs (estimated through fluid biomarkers) has been reported to be around 20 % (Pollak et al., 2018) and has been associated with clinical characteristics, such as worse cognitive performance and psychopathology (Campana et al., 2024; Najjar et al., 2017). However, the role of the BBB in the etiology and clinical trajectories of SSDs remains largely unclear. Bridging the gap between the periphery and the brain poses a significant challenge. Limited understanding of the BBB has hindered its direct targeting in diagnostic and therapeutic approaches.

Among in-vivo methods, dynamic contrast-enhanced MRI (DCE-MRI) stands out as a minimally invasive tool for detecting BBB breakdown. Unlike other approaches like Q_{Alb}, DCE-MRI provides specific assessment of BBB integrity, while also enabling localization of affected brain areas, with high spatial and temporal resolution (Montagne et al., 2015). It is based on the extravasation (leakage) of intravenously injected contrast agent (CA) into the extravascular space, enhancing image contrast that can be quantified. The efflux rate of the CA from plasma into brain tissue can be calculated through pharmacokinetic modeling of DCE T1-weighted MRI signal intensities. This approach enables quantification of various permeability measures, such as the BBB regional permeability constant, K_{trans}, that reflects the efflux rate (Candelario-Jalil et al., 2022; Sourbron and Buckley, 2013). It has been deemed the most advanced method for investigating subtle leakages (Wong et al., 2017; Chagnot et al., 2021; Heye et al., 2016), particularly favorable in BBB investigations in SSDs due to the low permeability values considered in this group (Larsson et al., 2009; Ewing and Bagher-Ebadian, 2013). DCE-MRI combined with kinetic modeling (i.e. the Patlak model) has been identified as the most accurate and appropriate method for quantifying subtle BBB leakage (Montagne et al., 2015; Cramer and Larsson, 2014).

In other neuropsychiatric disorders (e.g., Alzheimer's disease, mild cognitive impairment, and small vessel disease), DCE-MRI has proven to be a valuable tool for investigating the blood–brain barrier, revealing its permeability and leakage (Li et al., 2021; Zhang et al., 2019; Nehra et al., 2022). To date, only one study has investigated the BBB integrity in SSDs using DCE-MRI, though in a limited sample size, which hampers the detection of minimal BBB leakage in core regions of SSDs, due to a lack of statistical power. Cheng et al. reported higher K^{trans} values in the bilateral thalamus in a schizophrenia group (N = 29) compared to a healthy control group (N = 18), but these findings require further replication.

The present study significantly expands on this by utilizing the largest sample size to date (N = 81 individuals with SSDs and HC), which provides greater statistical power to investigate BBB permeability.

Our primary hypothesis is that individuals with SSDs will exhibit significantly increased BBB leakage in brain regions neuropathologically linked to the disorder (e.g. thalamus, hippocampus, prefrontal cortex, and cingulate cortex (DeLisi et al., 2006), aligning with prior postmortem and fluid biomarker studies suggesting CNS barrier disruption. Furthermore, we propose that BBB leakage may delineate a distinct clinical sub-phenotype within SSDs, characterized by worse cognitive performance and more severe psychopathology—similar to previously reported associations with barrier disruption (Campana et al., 2024; Cheng et al., 2022). Lastly, we hypothesize that BBB permeability will correlate positively with systemic inflammatory markers, given the evidence from postmortem, fluid-biomarker, and neuroimaging studies linking immune dysregulation to barrier dysfunction. Lastly, we hypothesize a positive association between BBB leakage and BCSFB dysfunction, as measured by QAlb. Given prior evidence suggesting that QAlb reflects barrier impairment in a subset of SSD patients, we expect that increased BBB permeability, as detected by DCE-MRI, will correspond with elevated QAlb values, indicating a broader pattern of CNS barrier dysfunction.

2. Methods and Materials

2.1. Subjects

A total of 45 (11 females) people with SSDs treated at the Department for Psychiatry and Psychotherapy of the LMU University Hospital, Munich, Germany, were enrolled between March 2022 and October 2023. Inclusion criteria comprised age between 18 and 60 years and a diagnosis of SSD, according to DSM-V, assessed with the Mini International Neuropsychiatric Interview (M.I.N.I.), German version 7.0.2 (Sheehan et al., 1998). All were inpatients, included at various stages of the subacute phase of their disorder. Eleven individuals had their first

episode psychosis, 15 were treatment-resistant, all were treated with antipsychotics during inclusion, mean duration of illness (DOI) was 109.96 (± 115.91) months and mean CPZ dose was 406.84 (± 271.41) mg per day. In addition, 42 age- and sex-matched HCs (11 females) were recruited via announcements in digital channels (e.g. homepage of the university hospital, social media) and enrolled between June 2022 and October 2023. HCs were defined as participants with no past or current self-reported psychiatric disorder (collected via interview). HC were also aged between 18 and 60 years. Four individuals with SSDs and two HCs were declared as dropouts and excluded from the analyses (reasons for dropout are explained in Supplementary Methods), resulting in a total of n = 41 individuals with SSDs (10 females, mean age: 35.17 ± 9.77 years) and n = 40 HCs (11 females, mean age: 33.55 ± 9.60 years) in our final analyses.

Detailed demographic data for both cohorts are presented in Tables 1 and 2.

Exclusion criteria for both groups were defined as follows: for SSD cohort: a primary psychiatric disorder other than SSD, current electroconvulsive therapy or non-invasive brain stimulation treatment, coercive treatment, acute suicidality, for both groups: any central nervous system (CNS) disorder, history of traumatic brain injury (TBI), severe somatic (e.g. inflammatory, rheumatic) diseases, acute infections, current pregnancy (excluded in clinical routine in the SSD cohort and via self-report in HC) or lactation, regular current drug abuse (in the past month, excluded via self-report and in the SSD group with additional clinical tox-screens when necessary), inability to provide informed consent, current participation in clinical trials and contraindication(s) to MRI or DCE-MRI, such as renal failure (assessed with Serum creatinine and estimated Glomerular Filtration Rate (eGFR)). Prior to inclusion in the study, all participants provided written informed consent. The study protocol was approved a priori by the local ethics committee of the Ludwig-Maximilian University Munich (reference number 21–1139). The study was conducted according to the Declaration of Helsinki.

Table 2
SSD group, disease characteristics.

	N	Mean	SD
Disease characteristics			
Diagnosis (DSM-V)	41	–	–
Schizophrenia	35	–	–
Schizoaffective disorder	5	–	–
Brief psychotic disorder	1	–	–
Duration of illness (DOI) (months)	41	109.96	115.91
Age at first symptoms (AFS) (yrs)	37	26.65	9.98
First episode (y: n)	11:30	–	–
TRS (y: n)	15:26	–	–
Andreasen remission criteria (y: n)	6:31	–	–
Antipsychotic treatment (y: n)	(41:0)	–	–
CPZ equivalent [mg per day]	41	406.84	271.41
Lifetime AP treatment (months)	41	87.57	110.11
GAF	41	49.78	12.51
Psychopathology			
PANSS total	38	62.47	13.00
PANSS positive	38	15.74	4.72
PANSS negative	38	15.08	5.28
PANSS general	38	31.66	6.18
Cognition			
TMT-A (sec)	32	33.31	13.67
TMT-B (sec)	32	92.78	64.35

2.2. CSF and blood acquisition

Only individuals with SSDs underwent basic blood test including complete blood count analyses as part of the clinical routine in our clinic (collected around 8 a.m.). Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) (ratios from absolute blood counts) were selected as inexpensive proxy markers indicative for inflammatory and immune-related processes as previously described in the literature (Ghobadi et al., 2022). Both NLR and MLR have been described as elevated in SSD (Karageorgiou et al., 2019; Özdin et al., 2017; Özdin and Böke, 2019), strengthening the role of immune-associated mechanisms of the disorder. The rations were calculated by dividing the absolute number of neutrophils and monocytes by the absolute number of lymphocytes per individual (Steiner et al., 2020). Absolute counts were obtained from clinical lab results, determined in our hospital laboratory using an automated counter (Sysmex Deutschland GmbH).

As part of standard SSD diagnostics in Germany, CSF examinations were offered to individuals with SSD, in accordance with the national schizophrenia guidelines (Gaebel et al., 2020) resulting in CSF collection from 25 individuals. Q_{Alb} (as a continuous variable) was selected as indicative for CSF pathology or BCSFB disruption and adjusted for age according to the formula: $Q_{Alb} = (4 + age/15) \times 10^{-3}$ (Reiber et al., 2001), age indicated as years. In all cases, CSF and serum were tested for neuronal autoantibodies (Supplementary Methods) to rule out autoimmune-mediated psychosis or encephalitis.

2.3. Demographic, clinical, and cognitive assessments

All individuals underwent basic demographic and clinical assessments (body mass index (BMI), total education, medication intake, somatic conditions, substance abuse, current smoking status), collected via interviews and questionnaires and, if possible, verified using medical records. In individuals with SSDs the following additional variables were collected through self-report and verified on medical reports: information on current antipsychotic medication (current daily antipsychotic medication on the day of DCE-MRI scans were converted to chlorpromazine equivalent doses (CPZ equivalent), according to the *Defined Daily Dose* method (Leucht et al., 2016), lifetime antipsychotic medication in months, duration of illness (DUI, defined as time period since first diagnosis), first-episode (FEP) or multi- episode psychosis (MEP)

Table 1
Demographic data of individuals included in the DCE-MRI analyses.

	N (SSD/HC)	SSDs 41		HCs 40		SSDs vs. HCs		
						Chi²	**df**	**p**
Demographics								
Sex (f: m)	81 (41/40)	10:31		11:29		0.004	1	0.95
Current smoking status (y: n)	81 (41/40)	22:18		5:35		14.31	1	**0.00015**
		Mean/ Median	**SD**	**Mean/ Median**	**SD**	**t/W***	**df**	**p**
Age (yrs)	81 (41/40)	35.17	9.77	33.55	9.60	897*	–	0.47
Total education (yrs)	77 (37/40)	14.84	3.59	18.39	2.14	–	57.73	**2.57e-06**
BMI (kg/m^2)	80 (40/40)	27.14	4.50	24.21	4.45	1110*	–	**0.0029**
Cognition								
TMT-A (sec)	72 (32/40)	33.31	13.67	23.10	6.36	933*	–	**0.0009**
TMT-B (sec)	72 (32/40)	92.78	64.34	54.55	19.02	954.5*	–	**0.0004**

BMI = Body-Mass Index, CPZ = Chlorpromazine, df = degrees of freedom, n = no, SD = standard deviation, TMT = Trail-Making Test, W = Wilcoxon rank-sum, y = yes, asterisk (*) highlighting where Wilcoxon rank-sum was used.

status (FEP being defined as first hospitalization due to psychotic symptoms). Cognitive performance was assessed with the Trail-Making Test (TMT, part A and B) in both groups. TMT assesses the cognitive elements attention, visual search and scanning, processing speed, task switching, cognitive flexibility and executive function (Bowie and Harvey, 2006) which are typically affected domains in SSDs. Patients additionally underwent the Mini International Neuropsychiatric Interview (M.I.N.I.) interview for diagnosis validation (Sheehan et al., 1998), a symptom severity assessment using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Global Assessment of Functioning (GAF) Scale (Suzuki et al., 2015).

2.4. Structural and DCE-MRI acquisition

MRI images were acquired on a 3-Tesla MRI scanner (3 T Magnetom Prisma, Siemens Healthcare GmbH) in the Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany, with a 64-channel head coil. **Supplementary Fig. S1** illustrates the data acquisition and analysis steps, while **Supplementary Table S1** details the scanning methodology.

The imaging protocol included T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) and T2-weighted sampling perfection with application optimized contrast using different flip angle evolution (SPACE) sequences for anatomical reference and clinical evaluation. The DCE sequence was used for leakage calculations. This sequence had a total scan time of 23 min and a voxel size of $1.8 \times 1.8 \times 1.8$ mm. During this sequence (after approximately 2 min, scanning time point 12/80), the gadolinium-based contrast agent (GBCA) (Gadobutrol, Gadovist®, Bayer AG, Leverkusen, Germany, 0.1 mmol/kg) was injected in the antecubital vein (injection rate 3 mL/s, followed by 25–30 mL saline flush). All scans were evaluated by an experienced neuroradiologist, and pathological scans were excluded from further analyses.

2.5. Data processing and analysis

2.5.1. Statistical analysis of demographics

The following tests were used to compare demographic characteristics between SSD and HC groups and clinical characteristics within the SSD cohort, with R (R version 4.1.2 (2021–11-01), Rstudio, version 2021.09.1 (RStudio Team (2020), 2020). Group differences in sample characteristics were explored with Chi-squared test for categorical variables, Welch's two sample *t*-test for normally distributed, and Mann–Whitney *U* test for non-normally distributed continuous variables. Normality within groups was assessed using the Shapiro-Wilk test. The threshold for statistical significance was set at a p-value < 0.05. Descriptive statistics are shown as mean ± standard deviation (Table 1).

2.5.2. Pharmacokinetic model analysis of DCE-MRI and K_{trans} maps

The DCE-MRI quantification and K_{trans} maps were calculated using the open-source software ROCKETSHIP v. 1.2, 2016 (Barnes et al., 2015), which runs on Matlab, and Patlak modeling (Patlak et al., 1983). Quantitative pharmacokinetic modeling was chosen for its ease of interpretation and reduced sensitivity to the acquisition protocol, enhancing comparability across studies and sites (Thrippleton et al., 2019). The Patlak method was selected due to the low expected permeability and hence low likelihood of back-diffusion (transport of contrast agent from brain tissue back to blood) that are prerequisites for the use of the Patlak method (Cramer and Larsson, 2014). Data processing in ROCKETSHIP included the following steps: Preparation of the dynamic datasets for DCE-MRI analysis, T1 mapping, selection of the arterial input function (AIF) or reference region (transversal sinus), noise filtering. The derived DCE-MRI parametric maps were based on the fitted AIF from the individual datasets. (For more details see Supplementary Methods).

2.6. DCE-MRI group comparisons

To compare the whole-brain leakage (K_{trans} parameter maps) across cohorts (SSDs vs. HCs (main hypothesis)), analyses were conducted using voxel-wise multiple regression or voxel-wise analysis of covariance (ANCOVA), including age, sex, BMI, smoking status and total education (in years) as covariates in line with current evidence for their implication in BBB disruption (Montagne et al., 2022; Mazzone et al., 2010; Feng et al., 2024; Weber and Clyne, 2021) and/or due to their significant difference between the cohorts. We then conducted linear regression analyses to investigate the leakage (K_{trans} value at each voxel) as predictor variable within the SSD group in relation to psychopathology (PANSS total/positive/negative/general), cognition (TMT-A, B), peripheral inflammatory markers (NLR, MLR)) and BCSFB pathology/breakdown (Q_{Alb}) as outcome variables, controlling for age, sex, BMI, smoking status and education. Significance threshold was set to voxel-wise alpha threshold of 0.001 and family-wise error (FWE) cluster correction at an alpha of 0.05 in all analyses. All analyses were conducted in SPM12.

A binary mask was generated by applying a threshold of 0.3 to the statistical contrast map using FSL's fslmaths tool. This thresholding procedure delineated regions of significant leakage for Cohen's d values > 0.3. ROIs (Regions of Interest) were selected from the Brainnetome atlas (Fan et al., 1991) and comprised anatomically defined whole brain regions. These ROIs were stored as individual binary masks in NIfTI (.nii.gz) format. The thresholded binary mask derived from the statistical contrast map served as a reference for determining the volume of activations within each ROI. For each ROI, the volume of activations was calculated in milliliters (ml) using FSL's fslstats tool with the −V option. This process involved isolating the voxels within each ROI that overlapped with the binary mask and computing their total volume. The resulting volume measurements represented the spatial extent of leakage within the respective ROIs. Furthermore, the percentage of activations relative to the total volume of each ROI was computed. This calculation provided a normalized measure of the proportion of activated voxels within each ROI, facilitating comparisons across different brain regions. As the Brainnetome atlas does not include specific brainstem regions, the Brainstem Navigator toolkit was used. The thresholded (voxel-wise alpha threshold of 0.001 and FWE cluster correction of alpha of 0.05) binary mask derived from the statistical contrast map served as a reference for determining the volume of activations within each ROI.

3. Results

3.1. Demographic data

A total of $n = 41$ individuals with SSDs (10 females, mean age: 35.17 ± 9.77 years) and n = 40 HCs (11 females, mean age: 33.55 ± 9.60 years) were included in our final analyses. Based on the only existing study to date, which reported differences in leakage using a sample of 29 individuals with SSDs compared to 18 HCs, this sample size was considered sufficient to detect differences between the groups. Individuals with SSDs had on average a significantly shorter period of education (in years) compared to HCs (14.84 vs. 18.39, $p = 2.57\text{e-}06$), higher BMI scores (27.14 vs. 24.21 kg/m^2, $p = 0.0029$) and worse cognitive function (TMT-A (33.31 vs. 23.10 sec, $p = 0.0009$) and TMT-B (92.78 vs. 54.55 sec, $p = 0.0004$)). Sex and age did not differ significantly between groups. Table 1 shows the demographic characteristics of the two groups and Table 2 the further characterization of the SSD cohort.

3.2. DCE-MRI (K_{trans}) group comparisons

The voxelwise K_{trans} map comparisons of the two cohorts (SSDs vs. HCs) at a whole brain level showed significantly higher K_{trans} signal

(leakage) in the SSD cohort compared to HCs (main hypothesis), when corrected for age, sex, BMI, smoking and total education. Fig. 1 illustrates the SSD/HC K_{trans} group comparison.

The K_{trans} values were calculated region-specifically based on the percentage and volumetric fraction (in ml) of the Brainnetome Atlas regions. The results for the ten regions with the highest values are shown in Fig. 2, results for all 246 Brainnetome regions can be found in **Supplementary table S2**.

The results for the ten regions with the highest values for brainstem regions are shown in **Supplementary Table S3**.

In order to evaluate the individual data distribution, K_{trans} mean values across all significant voxels were visualized and are shown in Fig. 3.

3.3. Within group (SSD) tests

Linear regression models, investigating the association of higher leakage (K_{trans}) and psychopathology/cognition (PANSS total, positive, negative, general; $n = 38$, TMT-A and TMT-B; $n = 32$), corrected for age, sex, BMI, smoking, total education, were performed and showed no significant associations.

Linear regressions investigating the association of higher leakage (K_{trans}) and peripheral inflammatory markers (NLR, MLR; $n = 41$), showed no significant results. Linear regression investigating the association of higher leakage (K_{trans}) and Q_{Alb} showed no association between higher K_{trans} values and Q_{Alb} ($n = 25$).

4. Discussion

This study aimed to investigate BBB leakage in the largest cohort of individuals with SSD to date, compared to HCs, using dynamic contrast-enhanced MRI (DCE-MRI).

Our study for the first time revealed significantly elevated K_{trans} values, in a widespread pattern, mostly affecting subcortical and cortical regions both limbic and fronto-temporal areas, indicating widespread BBB leakage in individuals with SSDs compared to HCs.

This finding aligns with the only other DCE-MRI study among individuals with SSD by Cheng et al., which reported higher BBB leakage in the thalamus among 29 individuals with SSDs compared to 18 HC (Cheng et al., 2022). Replicating this finding provides substantial evidence for BBB leakage in the thalamus, further substantiating its relevance in SSD pathophysiology. Disruption in the tightly regulated relationship between neuronal activity and blood flow (neurovascular coupling) can result in disturbed oxygen metabolism, neuronal death, and brain tissue atrophy (Sukumar et al., 2020). Thalamic leakage could thus play a key role in the context of already established structural (thalamic volume reduction), functional (disrupted functional connectivity), neurochemical (e.g. glutamatergic) and metabolic alterations (Adriano et al., 2010; Gong et al., 2019; Clinton and Meador-Woodruff, 2004).

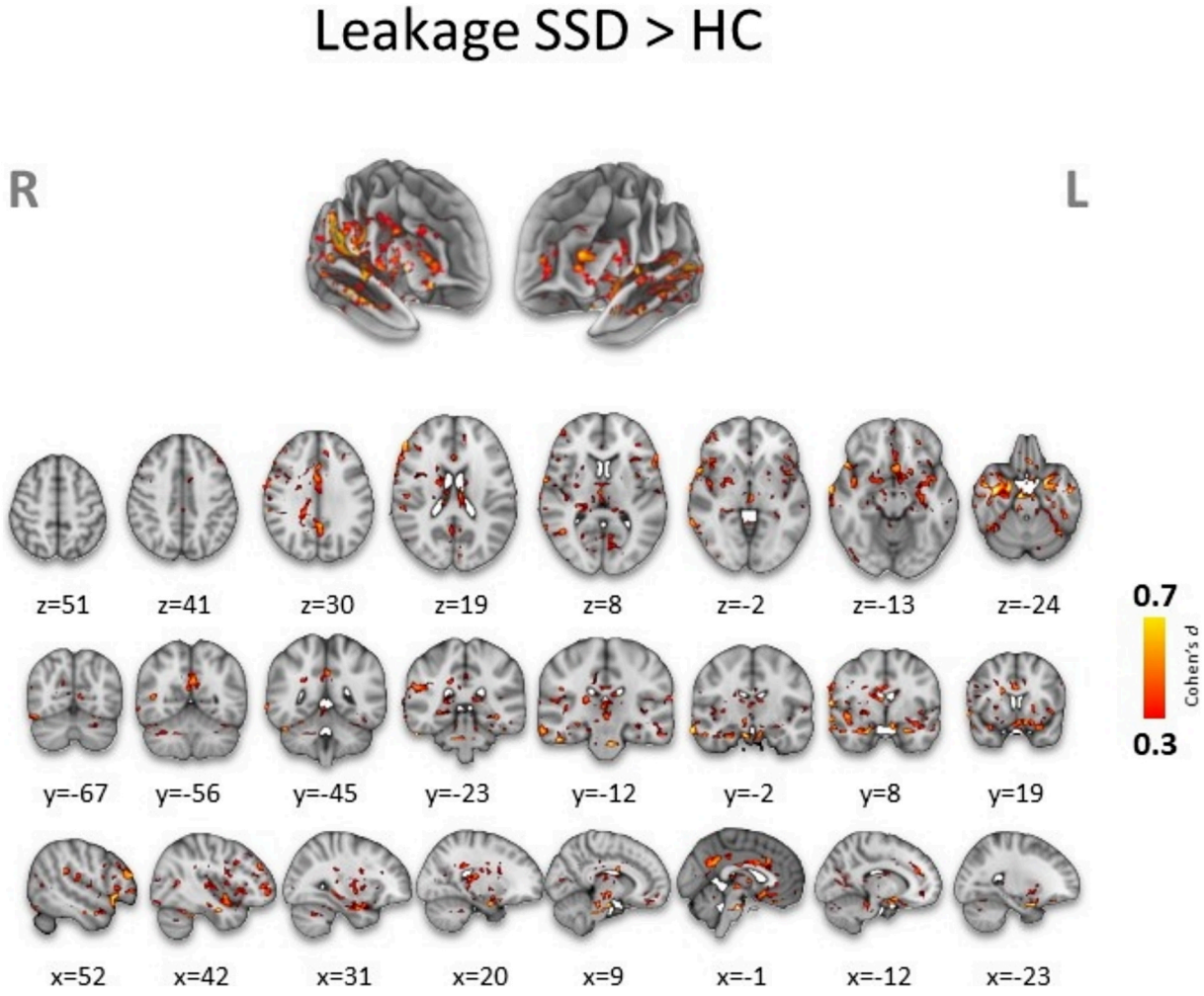
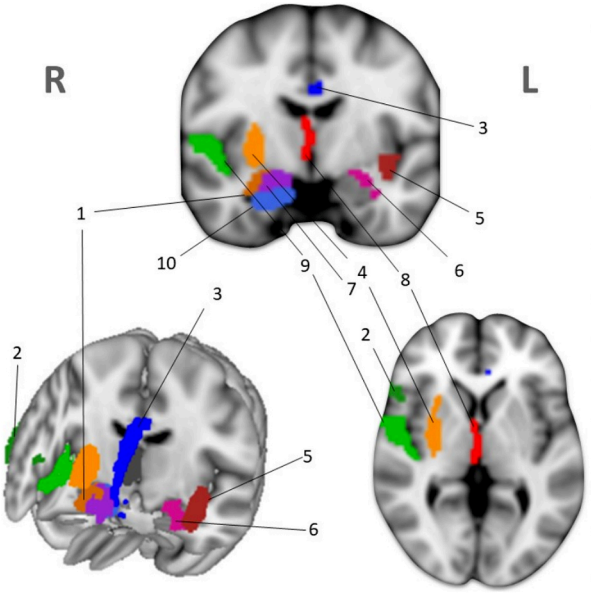


Fig. 1. K_{trans} map comparisons of the two cohorts (SSDs vs. HCs) showing higher widespread leakage in individuals with SSD compared to healthy controls (SPM12) colored signal represents brain voxels in which statistically significant higher leakage was detected in the SSD cohort compared to HC. K_{trans} values are shown thresholded for a Cohen's d between 0.3 and 0.7. The volumetric images are shown in axial z-orientation, coronal y-orientation and sagittal x-orientation with standard MNI spatial coordinates. Note: radiological convention, L = R and R = L.



No.	ROI name	ROI description	Volume in ml	Leakage in %
1	lAmyg R	lateral amygdala right	52	38.80
2	A45c R	inferior frontal gyrus right	142	37.96
3	A24rv L	limbic lobe, cingulate gyrus left	75	36.23
4	dlPu R	dorsolateral putamen right	138	34.41
5	vld-vlg L	insular gyrus left	89	34.09
6	lAmyg L	lateral amygdala left	28	32.55
7	mAmyg R	medial amygdala right	70	32.55
8	rTtha R	rostral temporal thalamus right	69	31.94
9	TE10-TE12 R	superior temporal gyrus right	228	31.27
10	rHipp R	rostral hippocampus right	139	28.77

Fig. 2. Top 10 Leakage ROIs. The ten ROIs with the highest leakage, presented by ROI name, ROI description, volume in ml, and leakage in per cent. Atlas used: Brainnetome. Note: representation in radiological convention L = R and R = L.

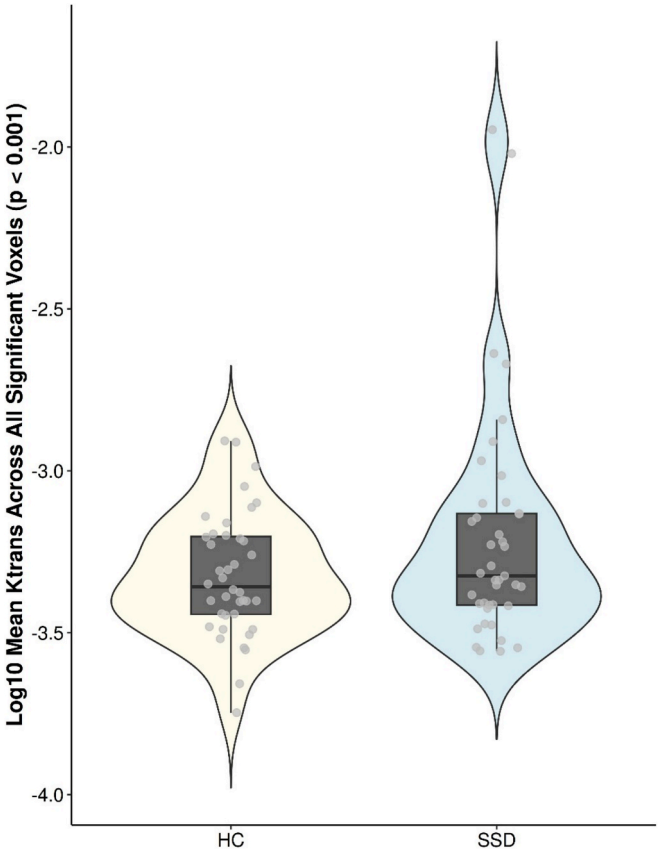


Fig. 3. Data distribution (log-transformed) of K_{trans} mean values across all significant voxels. Comparison of BBB leakage (K_{trans}) between SSD and HC show significant higher leakage in the SSD cohort. Data points represent individual log-transformed K_{trans} mean values, calculated for the significant clusters, in which leakage was detected in SSD compared to HC.

However, our study also detected leakage in additional brain regions such as the amygdala, cingulate, putamen, hippocampus, insular, frontal, and temporal regions, that are also presumed to be altered in SSD (van Erp et al., 2016). The broader pattern of leakage in our study compared to Cheng et al. may be attributed to a larger sample size, differences in methodology (e.g. longer scan duration of 22 min vs. 10 min in our protocol which enhances the detection of subtle barrier breakdown (Raja et al., 2018) and differences in cohort characteristics (e.g., younger subjects and shorter illness durations in Cheng et al.). Notably, BBB leakage in the hippocampus, another region majorly impacted in SSDs (van Erp et al., 2016), has previously been described in Alzheimeŕs disease (Montagne et al., 2015), another disorder marked by cognitive impairment, establishing a parallel between these disease entities.

Possible pathomechanistic factors contributing to the increased BBB permeability in SSDs include abnormalities in the macrovascular system (Schmidt-Kastner et al., 2012; Moises et al., 2015), the microcircuitry (Katsel et al., 2017) and in the regional cerebral blood flow (rCBF), i.e. hypoperfusion in frontal, temporal, parietal, cingulate, and thalamic regions leading to hypoxia (Sukumar et al., 2020; Katsel et al., 2017). Inflammatory processes are also key contributors, with circulating pro-inflammatory cytokines, such as TNF-alpha, commonly reported in schizophrenia (Halstead et al., 2023). These cytokines have been shown to affect the integrity of the BBB by altering astrocytic end-feet, a major component of the barrier, through the release of nitric oxide, as demonstrated in animal models (Farkas et al., 2006). On a smaller scale, capillary abnormalities, such as thickening, deformation, vacuolation of basal lamina, prominent swelling and vacuolation of astrocytic end-feet, alterations of pericapillary oligodendrocytes and signs of activation of microglial cells, have been described post-mortem (Uranova et al., 2010). Also, significantly reduced claudin-5 levels, a tight junction protein in SSD-relevant brain regions such as the hippocampal grey matter, and altered expression of junctional components, have been reported (Greene et al., 2020) (Uranova et al., 2010).

Interestingly, the main effect was driven by four individuals (~10 % of SSD patients). This is consistent with the heterogeneous nature of SSD, suggesting that BBB leakage may be a sub-phenotype observed in certain individuals rather than a characteristic of the disorder as a whole. This is also consistent with existing literature, which reports that 20–30 % of SSD patients exhibit blood-CSF barrier breakdown (e.g., via Q_{Alb}) (Pollak et al., 2018). This suggests that DCE-MRI offers a more specific and reliable method for assessing BBB disruption, as compared to Q_{Alb}, which has several limitations and is more susceptible to false

positives due to non-BBB-related factors that can elevate albumin levels (Yakimov et al., 2023; Pollak et al., 2020). The role of Q_{Alb} in evaluating BBB integrity should hence be strongly questioned in the research community.

Our study did not find a significant correlation between K_{trans} values and symptom severity (PANSS positive, negative, general, total). This is in contrast to the findings of Cheng et al., who reported significant correlations between BBB leakage and symptom severity. The discrepancy might be partially due to differences in study populations. In addition to the differences mentioned above the SSD cohort in the study of Cheng et al., showed on average a higher symptom burden compared to our cohort and almost half of them were antipsychotic-naïve, while all of our patients were treated with antipsychotic medication at the timepoint of the study. This possibly indicates that K_{trans} is a biomarker for psychopathology in the more acute (and severe) stages of disease. Of note, in line with our results, evidence on post-mortem ultrastructural changes in vasculature in SSDs also showed no association with clinical SSD subgroups (negative/positive symptoms, paranoid/nonparanoid types, different course of paranoid schizophrenia) (Uranova et al., 2010), further highlighting the difficulty to establish a clear link with clinical parameters. It is also possible that the PANSS subscale values were not sensitive enough to detect subtle associations with BBB leakage, warranting further research with more refined assessment tools, such as single-items in larger cohorts.

No studies have yet investigated the association between cognition and leakage in DCE-MRI in SSDs. Our findings, indicating a lack of association, are in contrast to available evidence in other psychiatric and non-psychiatric disease entities (e.g., Alzheimeŕs disease (AD), mild cognitive impairment, small vessel disease, systemic lupus erythematosus (Li et al., 2021; Zhang et al., 2019; Nehra et al., 2022; Kamintsky et al., 2020), which identified significant correlations between BBB leakage and cognitive decline. Notably, BBB leakage in the hippocampus in AD was associated with early cognitive dysfunction, irrespective of Alzheimer's Aβ and/or tau biomarker changes, suggesting that BBB breakdown is an early biomarker of human cognitive dysfunction in AD, independent of these disease-specific changes (Nation et al., 2019). However, the comparability of findings between these entities may be limited due to different underlying pathologies. The lack of association in our study may be due to the limited cognitive domains assessed by the TMT, suggesting that other cognitive domains could potentially show a correlation with K_{trans}. Additionally, within-cohort analyses may have been underpowered due to the small sample size. Missing data ($n = 9$) in cognitive assessments could have biased the results. The cross-sectional design may not fully capture the association between leakage and cognitive decline, as leakage may reflect an acute state (all participants were in inpatient treatment in both our study and Cheng et al.'s), while cognitive decline may manifest later, as observed in a longitudinal cohort (Kerkhofs et al., 2021). The lack of a clear correlation between BBB leakage and clinical outcomes highlights the complexity of SSDs and suggests that BBB leakage alone may not be a sufficient biomarker for symptom severity or cognitive impairment. Further research with prospective approaches applied in larger cohorts is urgently needed.

Our study showed no association between K_{trans} and Q_{Alb}, which represents BCSFB integrity. This finding is consistent with studies in different forms of dementia, where no correlation between BBB leakage (as measured by K_{trans}) and CSF/blood markers (e.g., Q_{Alb}) was reported (Hillmer et al., 2023). Possible reasons for this lack of correlation include structural and functional differences between the BBB and BCSFB (Yakimov et al., 2023), which might respond differently to pathological processes. Additionally, the low statistical power due to the small sample size of individuals with CSF in our study could have influenced the ability to detect significant associations between these biomarkers.

Similarly, the study found no significant correlation between K_{trans} values and MLR/NLR hindering an association between leakage and peripheral inflammation. There are no studies investigating this association in SSDs. There is however mounting evidence for an association between systemic inflammation and BBB leakage (Galea, 2021) and for inflammatory response following BBB disruption, through the activation of glial cells (microglia and astrocytes) that triggers the release of proinflammatory cytokines, leading to neurotoxicity (Takata et al., 2021). Potential explanations for the absence of correlation in our study include the inherent limitations of peripheral biomarkers in capturing nuanced alterations in BBB integrity or central nervous system inflammation. Additionally, these ratios predominantly mirror the *cellular* immune response, which may not directly correspond to the subtle pathophysiological changes we sought to measure.

The lack of association between BBB leakage and peripheral CSF/inflammatory markers underscores the difficulty in bridging the brain and the periphery, especially in the context of *subtle* inflammatory mechanisms. It also highlights the importance of distinguishing CNS barriers and their roles in SSD pathology, emphasizing the need for more specific BBB integrity biomarkers.

Limitations.

Our findings must be interpreted with caution. Firstly, although we corrected our statistical models for BMI and smoking, we did not correct for all cardiovascular disease risk factors (CVDRF) that could mediate BBB disruption. Future studies should aim to incorporate a more comprehensive adjustment for cardiovascular risk factors to better understand their impact on BBB integrity in SSDs. Additionally, we did not selectively include or stratify patients based on known inflammatory markers, despite evidence that a subset (~40 %) of patients may exhibit elevated levels (Boerrigter et al., 2017). This may have influenced our ability to detect cellular and molecular correlates of BBB disruption. Future research should consider stratification based on inflammatory status to better delineate its role in BBB integrity. Further limitations involve a sampling bias, since not all individuals with SSDs were eligible for inclusion in our single-site study. We did not standardize inclusion based on the acuteness of the disorder, which might have impeded interpretation of the results in regards to the stage of the disorder. Our cohort did not include medication-naïve individuals with SSDs and thus the magnitude of the effect that antipsychotic treatment potentially had on our findings cannot be measured. Future studies should include medication-naive individuals. Additionally, there was an underrepresentation of female participants, which could affect the generalizability of our findings. Another limitation pertains to the method of pharmacokinetic models used, which are based on a highly simplified description of tissue microstructure and function and can hence ignore potentially relevant features such as interstitial fluid transport (Thrippleton et al., 2019). However, the combination of DCE-MRI with the Patlak model has been described as the method of choice in permeability imaging with expected subtle leakage (Cramer and Larsson, 2014) Although this study included the largest SSD cohort to date undergoing DCE-MRI compared to HCs, our sample size for subgroup analyses remained relatively small. Future studies with larger sample sizes should focus on individual case-level analyses to better understand the clinical characteristics of the most affected individuals. Lastly, the cross-sectional nature of the approach does not allow conclusions on dynamic changes in the BBB that possibly underly the disorder. Larger longitudinal, multimodal studies, that investigate the temporal relationship between BBB impairment and symptom severity, combined with vascular and BBB genomics are essential to robustly replicate our findings and comprehend the relevance and dynamics of BBB disturbances in SSDs.

4.1. Conclusion

Our findings provide robust evidence for widespread BBB leakage in SSDs compared to HCs, extending beyond the thalamus to multiple brain regions associated with SSDs. Compared to the only available study to date (Cheng et al., 2022), which included 29 SSDs and 18 HCs, this study nearly doubles that sample size to 82, making it the largest cross-

sectional DCE-MRI study in SSDs to date. This increase in sample size enhances statistical power, allowing for a more thorough investigation of subtle BBB changes in regions beyond the thalamus. Our study further covers a broad spectrum of assessments, including psychopathology, cognition, disease progression, blood derived immune-related and CSF markers. Additionally, it is the first study to conduct DCE-MRI with a sufficient sequence duration to detect minimal leakage in SSDs. Our findings validate the hypothesis of BBB disruption in SSDs and underscore the potential of DCE-MRI as a valuable diagnostic tool for this disorder. Understanding the role of the BBB in SSDs could open avenues for targeted interventions aimed at preserving or restoring BBB integrity. Moreover, the integration of DCE-MRI assessments of BBB integrity with existing diagnostic tools holds promise for enhancing early detection of biological mechanisms in SSDs.

5. Code availability

All software packages used in this study are publicly available: Rocketship v1.2 2016 (https://github.com/petmri/ROCKETSHIP/blob/master/dce/compare_gui.m), FSL v. 6.0.5.1 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslInstallation), SPM12, v. 7771 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).

Author contributions

EW, DK and JM designed and conceptualized the study. EW, DK, JM designed this study and wrote the protocol. JM recruited patients and collected study data. DK and KS trained staff on MRI assessments. MRI acquisition were performed by JM, JuM, BP, IL. MRI preprocessing was performed by HT, IL. NF supervised and performed MRI data analysis. All statistical analyses were performed by LR, NF and JM. Data visualization was performed by NF and LR. JM wrote the first draft of the manuscript. All authors contributed to and approved the final version of the manuscript.

CRediT authorship contribution statement

Joanna Moussiopoulou: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Vladislav Yakimov:** Writing – review & editing, Methodology, Investigation. **Lukas Roell:** Writing – review & editing, Software, Methodology, Investigation, Data curation. **Boris-Stephan Rauchmann:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Hannah Toth:** Writing – review & editing, Investigation, Formal analysis. **Julian Melcher:** Writing – review & editing, Investigation. **Iris Jäger:** Writing – review & editing, Investigation. **Isabel Lutz:** Writing – review & editing, Software, Methodology, Investigation, Data curation. **Marcel S. Kallweit:** Writing – review & editing, Investigation, Formal analysis. **Boris Papazov:** Writing – review & editing, Software, Methodology, Investigation. **Emanuel Boudriot:** Writing – review & editing. **Klaus Seelos:** Writing – review & editing, Methodology. **Amir Dehsarvi:** Writing – review & editing, Methodology, Formal analysis. **Mattia Campana:** Writing – review & editing, Investigation. **Florian Raabe:** Writing – review & editing, Methodology. **Isabel Maurus:** Writing – review & editing. **Lisa Löhrs:** Writing – review & editing. **Matthias Brendel:** Writing – review & editing. **Sophia Stöcklein:** Writing – review & editing, Methodology. **Peter Falkai:** Writing – review & editing, Supervision, Resources, Project administration, Investigation. **Alkomiet Hasan:** Writing – review & editing. **CDP Working Group:** Writing – review & editing, Investigation. **Nicolai Franzmeier:** Writing – review & editing, Visualization, Supervision, Software, Formal analysis. **Daniel Keeser:** Writing – review & editing, Visualization, Supervision, Software, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Elias Wagner:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.04.003.

Data availability

The de-identified data of this study will be made available in BIDS format upon publication in the Open Neuro repository (https://openneuro.org/) (link accessible after acceptance of the manuscript).

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