**Imaging Blood Brain Barrier Dysfunction in Drug -Resistant Epilepsy: A Multi-Center Feasibility Study**

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**Abbreviations:** BBBD = Blood brain barrier dysfunction; DCE = Dynamic contrast enhanced; MRI = Magnetic resonance imaging; DRE = Drug resistance epilepsy; PWE = Patients with epilepsy

***Word limit\*: 6000***

***Abstract word limit:* 400**

**Abstract:**

The dysfunction of the blood-brain barrier (BBBD) has been linked to various neurological disorders, including epilepsy. BBBD has been observed in tissue resected from patients with drug-resistant epilepsy (PWE) who had undergone surgery. In this study, we utilized dynamic contrast-enhanced MRI (DCE-MRI) to identify brain regions with BBBD in PWE as compared to healthy individuals. We scanned 50 PWE and 58 controls from four different epilepsy centers. PWE had a significantly greater brain volume and a higher number of brain regions with BBBD compared to the healthy controls (p<0.00001). No differences were observed between patients diagnosed with focal seizures and those with idiopathic generalized epilepsy, although the specific affected regions differed. No significant differences were identified in patients with lesions visible on MRI compared to those without lesions. BBBD was observed in brain regions suspected to be related to the onset of seizures in XX% of patients (N=). These findings support previous pre-clinical studies on the role of BBBD in the development of epilepsy and drug resistance, and as a potential target for the treatment of epilepsy. Additional research is necessary to confirm the usefulness of DCE-MRI in the early diagnosis of drug-resistant epilepsy and the identification of the seizure-onset zone during pre-surgical assessment.

**Introduction**

Blood brain barrier dysfunction (BBBD) has been reported in various neurological disorders, including epilepsy. The impact of BBBD on neural networks is not fully understood, but recent studies on experimental rodents have shown that disrupting the BBB or exposure of brain cells to serum albumin (and likely other proteins) lead to the activation of TGFβ signaling in astrocytes. This activation results in astrocyte transformation that fail to maintain extracellular homeostasis, including the maintenance of physiological concentrations of potassium and glutamat (David et al). In addition, transformed astrocytes are release inflammatory cytokines as part of activation of the brain's innate immune response, followed by alterations in the extracellular matrix (Kim et al., 2016), excitatory synaptogenesis (Weissberg et al., 2015), pathological plasticity (Salar et al., 2016), and delayed neurodegeneration (Tomkins et al., 2007). These cascading effects ultimately lead to dysfunction of the local neural network and the occurrence of spontaneous seizures as well as drug resistance when BBBD persists (Salar et al., 2016).

Such role of BBBD in drug-resistance epilepsy has been supported by neuropathological studies showing serum proteins (including albumin), phosphorylated SMAD2 in astrocytes (due to TGF signaling) and neuroinflammation in tissue resected from patients with drug-resistance epilepsy (PWE). In addition, seizure-induced BBBD has been shown in PWE when scanned up to 180min following a seiure. However, no in-vivo human studies could confirm inter-ictal BBBD and its relation to the seizure onset zone. In recent years, dynamic contrast-enhanced MRI (DCE-MRI) has become the most common approach to quantify the extent and localization of BBBD in human patients [(Weissberg et al., 2014)](https://paperpile.com/c/lBqL0o/0Pxl).. The Veksler linear model has been shown to allow the detection of a *slow* (more subtle) BBB leakage (measured ~6-20 min after contrast injection) [(Lublinsky et al., 2019; Merali et al., 2017; Rüber et al., 2018; Veksler et al., 2020; Villringer et al., 2017)](https://paperpile.com/c/lBqL0o/LawR+tVpa+hFHS+Y7FA+9got). Pre-clinical and clinical studies confirmed that such subtle BBBD can be quantitatively measured under different brain pathologies and experimental models, and have suggested that it represents an increase in trans-cellular leakage through the compromised barrier [(Bar-Klein et al., 2017; Kamintsky, Beyea, et al., 2020; Kamintsky, Cairns, et al., 2020; Serlin et al., 2019; Vazana et al., 2016; Weissberg et al., 2014)](https://paperpile.com/c/lBqL0o/VaAj+pnIv+WBsm+0Pxl+93x4+MghD), although the role of tight junction down-regulation has also been suggested *(Cambell Nature Comm paper).* Studies in canines with idiopathic epilepsy (IE) further showed prominent BBBD, espeically in temporal brain regions compared with healthy dogs [(Hanael et al., 2019)](https://paperpile.com/c/lBqL0o/Mzw2). We therefore tested the role of DCE-MRI in the identification of brain regions with BBBD in PWE in four different epilepsy centers using a similar protocol and centered blinded analysis.

**Materials and methods**

**Human subjects**

The study was approved by the Ethics Committee of Soroka Medical Center, Beer Sheva, Israel (SUMC), Beilinson, Dublin, UK, Dalhousie. ADD THE CENTERS FULL NAME AND SHORT CUTS HERE…. Written informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards.

**Healthy Participants**

We included 58 volunteers who were recruited as healthy controls (mean age = 28.94 ± 5.08, 48.28% male). Among them 43 were scanned in SUMC , 8 were scanned in Dalhosuie University (Halifax First Seizure Clinic, HFSC) and 7 were scanned in National Hospital for Neurology and Neurosurgery and Chalfont Centre for Epilepsy (London, CCE). Inclusion criteria encompassed individuals aged 18 to 90 years, with no known illness or history of a neurological or psychiatric disorder, and normal kidney functions in a recent blood test (< 3 months prior to scanning). Exclusion criteria included individuals with contraindications for an MRI scan.

**Patients with epilepsy**

Out of 50 PWE (mean age = 33.64 ± 13.51, 58.00% male) who were recruited to the study 27 were scanned in SUMC, 11 in HFSC, 6 at the TC and at 6 at CCE. Patients were randomly recruited as part of follow-up in the respective epilepsy clinic. Inclusion criteria were: (1) between 18 to 90 years of age. (2) had a medically documented history of seizures according to the ILAE classification of epilepsy. (3) patients underwent routine laboratory and clinical follow-ups. (4) underwent at least one electroencephalogram evaluation by a neurology expert. (5) patients were considered drug-resistance as they continued to suffer from seizures despite extensive and continuous treatment of several anti-seizure medications (ASMs, Table X).

**Magnetic Resonance Imaging**

All participants were subjected to MRI scans utilizing a 3T MRI machine. Scanning was done at least 72 hours after the last reported seizure. In addition to routine clinical sequences (T1, T2, FLAIR….), participants underwent a similar DCE-MRI protocol as detailed previously (Veksler et al., 2020). For more details see Table 2.

**BBB Permeability analysis**

Assessment of BBBD was done using in-house Matlab scripts as has been reported [(Chassidim et al., 2013; Friedman et al., n.d.; Kamintsky, Beyea, et al., 2020; Serlin et al., 2019; **Veksler et al., 2020**)](https://paperpile.com/c/lBqL0o/VaAj+WBsm+zaCI+rysy). In short, images were registered and normalized to MNI coordinates using SPM12 (<http://www>.fil.ion.ucl. ac.uk/spm). BBB permeability maps were created for all subjects by fitting a linear model and calculating the slope of contrast agent concentration in each voxel from minute 6 after injection of the Gd-based contrast agent until the last volume in the DCE-MRI (3 to 20, number of volumes -YY, see Table 2) . To account for inter-individual variability in contrast flow to the brain, each individual slope was normalized to the slope measured in the superior sagittal sinus [(Veksler et al., 2020)](https://paperpile.com/c/lBqL0o/LawR). BBBD was defined if the slope value was higher then the 95th percentile of all slopes in a healthy controls. The percentage of brain volume with suprathreshold voxels was used as a measure of overall brain volume with BBBD. Region specific BBBD analysis was done using brain segmentation to 126 regions based on the MNI brain atlas (<https://github.com/neurodebian/spm12/tree/master/tpm>). For each region, a separate threshold for BBBD was defined (95th of controls value for the same region).

**Statistical analysis**

Continuous variables are expressed as means ± SEM?. Normally distributed variables were tested by Welch’s t test. Mann-Whitney and Kruskal-Wallis tests were applied for comparison of unpaired nonparametric data sets. Wilcoxon signed-rank test was used for paired nonparametric data sets. Categorical variables are reported as frequencies and percentages and were tested by χ2 test or Fisher’s exact test. Statistical significance was determined when two sided p value ≤ 0.05. For correlations the Pearson method was used. Linear regressions were used to calculate the effect of age and sex on permeability. Z-score was calculated based on standard deviations of controls : where y is the value (i.e averaged slope in any given region) and x is the mean value in healthy controls for the same region, sdv(x) is the standard deviation of slope values within the same region in healthy controls. Regions with Z-score > 2 were considered to have BBBD. A one-way ANOVA was used to find interactions between age group, sex and permeability. Corrections for multiple comparisons were performed by running Benjamin and Hochberg false discovery rate method[(Benjamini & Hochberg, 1995; Storey, 2002)](https://paperpile.com/c/lBqL0o/May7+f18y).

**Data availability**

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

**Results**

**Patients with epilepsy frequently present with BBBD**

Out of 50 PWE recruited for the present study, 40 had a clinical diagnosis of seizures with focal onset (mean age = 34.35 ± 13.25 years, 65.00% male), and 10 were clinically diagnosed with generalized seizures (mean age = 30.80 ± 14.87, 30.00% male). Based on semiology and interictal and/or long-term EEG monitoring, 24 PWE (32.54 ± 12.33 years, 66.67% male) the ictal onset zone was suspected in the temporal lobe, in 14 patients within the frontal lobe (38.21 ± 15.72 years, 50.00% male) ,one 22yo male parietal lobe and one 29yo male unknown.

BBBD maps were created to each patients and were superimposed on T1 images, showing voxels with a Z-score > 2 compared with controls as voxels with BBBD (Fig. 1A). In addition, regional analysis revealed anatomical brain regions with BBBD (mean regional permeability Z score > 2, see Methods and Figure 1B) – allowing a better characterization of brain regions showing BBBD. PWE has higher brain volume with BBBD compared with controls (11.79 ± 7.26% compared with 4.80 ± 2.62%, p<10^-8). On regional analysis, PWE had on the average XX+- brain regions with BBBD compared with none in controls (p<) with at least one brain region with BBBD in XX out of 50 patients. There was no significant differences in age (p=0.39) or gender (p=0.29) between controls and PWE.

No significant differences were found between brain volume with BBBD or averaged Z score and patients age (p = >0.5) as well as disease age of onset (p > 0.25) or duration of disease (p > 0.07).

**Regional Analysis reveals brain regions more likely to show BBBD:**

While we found large differences between individual PWE in the extent and distribution of BBBD, a group comparison showed an averaged Z score > 2 in 15 brain regions (mostly cortical gray matter), of whom 9 were within the frontal and temporal lobes (Fig. 2A). Regions included the Left supramarginal gyrus (Z=2.61), Right inferior temporal gyrus (2.26), Right cuneus (2.23), Left central operculum (2.2), Right middle frontal gyrus (2.19), Right Cerebral White Matter (2.16), Left planum temporale (2.16), Right supplementary motor cortex (2.14), Left angular gyrus (2.12), Left frontal pole (2.12), Right and left orbital part of the inferior frontal gyrus (2.09 and 2.08, respectively), Right transverse temporal gyrus (2.08), Right superior frontal gyrus medial segment (2.05), and Left parietal operculum (2.0). Statistical comparison showed a significance increase in permeability in xx out of 126 regions (which test, Fig. 2B, E)

**BBBD is common in both focal and generalized epilepsy**

No significant differences were found in total brain volume with BBBD between patients with focal and generalized epilepsy (12.20 ± 7.66% vs. 14.28 ± 5.67% brain volume with BBBD, respectively, p=???), both groups significantly higher than controls (p<0.0000). Regional analysis revealed xx regions the focal group compared with yy regions in the generalized group with a Z >2 (Fig. 2 F-G, Table S2). Interestingly, patients clinically diagnosed with suspected temporal lobe epilepsy had xx regions with a Z score > 2 including

LIST OF REGIONS ??? .

**MR-positive lesions**

In xx patients neuroradiological assessment of clinical MR sequences revealed a pathology, including ADD A LIST (N= YY for each pathology). BBBD was most often predominant within the same hemisphere of the observed lesion (N=) or close to the lesion it self (“peri-lesional, N=, Fig. 3A). However in XX cases BBBD was on both hemispheres (Fig. 3B, N=) or unrelated to the lesion location (Fig 3C, N=) (Fig. 3D). No significant differences were found between lesional and lesion-negative MRIs in the extent of BBBD (33.82 ± 27.27 vs. 25.67 ± 22.20% p=0.33) or averaged Z score (ADD NUMBER, p=0.33) (Fig. 3E-F).

**Medications**

All patients in this cohort were treated with anti-seizure medications (Table X). No significant differences were found in the extent (brain volume with BBBD or averaged Z score) or number of affected regions between patients who were prescribed with one (N=), two (N=) or more (N=) different anti-seizure medications (13.60 ± 7.27, 33.94 ± 23.57 and xx +- yy%, respectively, p=0.62; Z score ADD NUMBERS, p = ???). In an effort to test whether the extent of BBBD (% brain volume or Z score) patients were grouped into high (% volume with BBBD above median, N= ADD % and NUMBERS ) and low ((% volume with BBBD above median, N= ADD % and NUMBERS) BBBD. No differences were found between the groups in number of prescribed ASMs or any single drug, except clobasam….. ADD DATA ? (Supp Figure ?)

**Discussion**

In this study, we provide evidence for the presence of an interictal leaky blood-brain barrier (BBBD) in patients with drug-resistant epilepsy. Our findings build upon previous imaging studies in epileptic dogs and align with studies in experimental rodents (refs). While DCE-MRI has previously been used to assess BBBD in various neurological conditions, its impact on disease presentation and progression remains unknown. However, some studies suggest that patients with traumatic brain injury and a compromised BBB are more likely to develop a recurrent stroke (Serlin) and post-traumatic epilepsy (Tomkins JNNP). Bipolar patients with extensive BBBD were more likely to present with insulin resistance and neuroprogression (Kamintsky), sand patients with systemic lupus erythematosus are more likely to show cognitive deficits (Kaminsteky).

This is the first study which aims to delineate the extent and spatial distribution of BBBD in an individual patient based on data from healthy controls, with the goal of establishing a new diagnostic and prognostic biomarker in epilepsy. Regional analysis suggests that certain brain regions, particularly cortical gray matter in the frontotemporal lobes, are more likely to exhibit BBBD in PWE. This aligns with findings in rodent models of temporal lobe epilepsy and canine epilepsy *(Bar-Klein 2017, Hanael, 2019*), supporting a link between BBBD and disease pathogenesis, potentially in regions with a lower seizure threshold. Additionally, cases where BBBD occurs near MR-detected epileptogenic lesions (e.g. hippocampal sclerosis – Fig. X), further support this relationship.

In our cohort, in a few patients BBBD could span multiple brain regions, entire hemisphere (or both hemispheres, Fig. XX) even in patients presumed to have focal epilepsy. This may be due to a role for a compromised BBB in seizure propagation and/or comorbidities, in addition to its contribution to ictogenesis. Notably, we cannot rule out that widespread BBBD was due to a recent unreported seizures (Ruber Brain), metabolic disorders (Kaminstky), or unrelated small vessel disease (Serlin, others ???). Larger studies should explore the impact of BBBD on comorbidities, such as depression, the coexistence of metabolic disorders like insulin resistance. Future study on the correlation between BBBD extent and localization and postoperative seizure freedom might shed light on the role of DCE-MRI in pre-surgical assessment.

Interestingly, we did not find significant differences in the extent of BBBD between patients diagnosed with focal and those with generalized seizures . Together with the observation that patients with generalized seizures had a higher number of brain regions with BBBD, support the notion that "generalized seizures" may originate from fast-spreading seizures from an unknown focus, rather than distinct origins (Gauffin et al., 2021; Seneviratne et al., 2014). .

The high prevalence of BBBD in our cohort could be influenced by a sampling bias, as patients included in this study experienced frequent seizures despite treatment with ASMs. Future studies should investigate BBBD in patients who are seizure-free or in the early stages of the disease before starting medications. If such bias exists in our cohort the high BBBD occurrence could be related to higher seizure frequency, effect of drugs or related to drug resistance in our cohort. We found no correlation between BBBD extent or spatial distribution to seizure frequency or the number of prescribed ASMs. Interestingly, a small group of patients (N=) who were treated with the 1,5‐benzodiazepine, clobazam, were more frequent in patients in the high BBBD group (>50% of brain volume with BBBD) compared with the patients with relatively low brain volume with BBBD. Whether benzodiazepines have a direct effect on BBB integrity is not known (but see ref) and might worth future investigation. BBBD in experimental animals and human epileptic tissue surgically resected has been previously shown to be associated with the presence of serum albumin within the brain neuropil (refs). Interestingly, exposing brain tissue to serum albumin in rodents was shown to acutely reduce seizure threshold (ref), underlie epileptogenesis and delayed spontaneous seizures (Seiffert, Ivens, Bar-Klein, Weissberg), and induces resistance to anti-seizure medications in brain slices exposed to 4-aminopyridine (4-AP) (Salar et al). Albumin-induced drug-resistance could be simply caused by reduced free levels of ASMs which bind to albumin. Future studies in drug-responsive, seizure-free PWE is awaited to further explore this hypothesis. Our study does support, however, the notion that therapeutic targeting BBBD may become a novel therapeutic approach for drug-resistance patients.

In conclusion, our study introduces a new quantitative method for assessing the extent and distribution of BBB disruption in individual epilepsy patients and confirms the frequent occurrence of a compromised BBB. These findings support the use of DCE-MRI as an additional tool for diagnosing the seizure onset zone during pre-surgical assessment. Larger studies are necessary to uncover the role of BBB imaging in the diagnosis, prognosis of drug resistance, and surgical outcomes in patients with epilepsy.

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**Competing interests**

The authors report no competing interests.

**Figures**

**Tables**

**Table 1** DCE-MRI acquisition protocols for each institution and the number of scans made.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Institution** | **3T MRI Machine** | **Δt, sec** | **Voxel size, mm** | **Acq. Matrix** | **FOV, cm** | **DCE: TE/TR, FA** | **Variable Flip Angles (FA), TE/TR** | **Constast agent** | **Number of PWE** | **Number of controls** |
| BGU/TAU | Philips Ingenia | 20 | 0.9x0.9x6 | 192x187x27 | 20 | FFE,2/4,60 | 5-15-20-25 ° DESPOT1, 2/4 ms | Dotarem® | 27 | 43 |
| DAL/NSHA | Discovery MR750 | 20 | 1.25×1.25×6 | 192×192×34 | 24 | LAVA, 2/4 150 | 5-10-30° DESPOT1, 2/10 ms | MultiHance | 11 | 8 |
| UCL | General Electric (Boston, MA) |  | 1x1x8 |  | 24 |  |  | Prohance | 6 | 7 |
| TRC | Philips Achieva | 6.4 | 1×1.3×5.0 | 240×123 |  | FFE, 2.8/5.7, 60 | 2-10-16-240, FFE,2.78/5.67 | MultiHance | 6 | 0 |

**Table 2** Demographics and clinical data.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Controls N = 58** | **Epilepsy N=50** | **Focal N=40** | **Generalized N=10** | **Temporal N=24** |
| **Gender, female %** | 51.72 | 40 | 32.5 | 70 | 31.82 |
| **Age , years (std)** | 28.94 (5.08) | 33.64 (13.51) | 34.35 (13.25) | 30.80 (14.87) | 31.95 (12.70) |
| **Age at onset median, years (range)** |  | 16.50 (1.5-63) | 17.00 (1.5-63) | 13.00 (3-23) | 17.00 (2-31) |
| **Epilepsy duration , median, years (range)** |  | 15.00 (0-55) | 14.50 (0-44) | 17.00 (0-55) | 13.00 (0-44) |
| **Polytherapy %** |  | 66 | 75 | 30 | 81.81 |
| **Lesional %** |  | 46.29 | 45 | 30 | 59.09 |

**Supplementary material**

**Supplementary Table**

**Table S1** lesions data per PWE

|  |  |  |  |
| --- | --- | --- | --- |
| Number | MRI finding | BBB finding | Clinical Diagnosis |
| 1 | Focal hemosidering, Lt. occipital & parietal | Rt. Fronto-Temporal | GTCE |
| 2 | Frontal cortical dysplasia, Lt. | Lt. Fronto-Parietal | Frontal lobe, with nocturnal complex partial seizures. |
| 3 | White matter lesion (Rt. Superior frontal) | Rt. Hemisphere (diffuse) | Myoclonic |
| 4 | Rt. Hippocampal atrophy | Bilateral: Lt. Amygdala, Lt. Hippocampus, Rt. Frontal | Focal, unknown. |
| 5 | Old Infarct (Lt. basal nuclei) with white matter changes | Lt. Parieto-Temporal | Lt. Frontal/Temporal |
| 6 | [Heterotropia & Schizencephaly](https://www.google.com/search?sca_esv=583659685&sxsrf=AM9HkKmSZmnWnafGzipfVfNYz8FFW5KGqw:1700338409193&q=Schizencephaly&spell=1&sa=X&ved=2ahUKEwi82oKXrs6CAxUvpIkEHazDDNkQkeECKAB6BAgIEAI) Rt. Parietal | Rt. Temporo-Occipital | TLE, Susp. Lt. |
| 7 | Cortical malformation, Lt. Frontal | Lt. Frontal, Bilateral Temporal | Multi focal epilepsy Susp. Lt. frontal' |
| 8 | Post-surgical removal of cavernoma, Lt. Parietal | No BBBD | TLE, Lt. |
| 9 | Hippocampal sclerosis, Lt. | Lt. Temporal | Lt. Temporal |
| 10 | Small vessel disease, bilateral | Bilateral Diffuse | Focal epilepsy without impaired awareness. |
| 11 | Temporal lobe cavernoma, Lt. | Bilateral Fronto-Temporal | Generalized |
| 12 | Gliotic changes, post removal of AVM, Rt. Parietal | Bilateral diffuse | Frontal |
| 13 | Rt. Hippocampal sclerosis | Bilateral Temporal | TLE, Rt. |
| 14 | Rt. Hippocampal sclerosis | Bilateral Temporal. Rt. > Lt. | TLE, Rt. |
| 15 | Lt. Hippocampal atrophy | Bilateral Temporal | TLE, Lt. |
| 16 | Lt. Hippocampal sclerosis | Rt. Frontal | TLE, Rt. |
| 17 | Lt. Hippocampal sclerosis | Lt. Hippocampus | TLE, Lt. |
| 18 | Lt. temporal atrophy | Lt. Inferior frontal gyrus | TLE, Lt. |
| 19 | Rt. Hippocampal sclerosis | Rt. Frontal | TLE, Rt. |
| 20 | Lt. Hippocampal sclerosis | Lt. Fronto-temporal | TLE, Lt. |

**Table S2** Z-score per region

|  |  |  |  |
| --- | --- | --- | --- |
| **Region** | **All** | **Focal Epilepsy** | **Generalized Epilepsy** |
| **Left superior parietal lobule** | 2.491478 | 3.056438 | 2.31566 |
| **Left Putamen** | 2.039788 | 2.264965 | 2.265581 |
| **Right inferior temporal gyrus** | 2.030457 | 2.102124 | 4.506394 |
| **Left Cerebral White Matter** | 2.021026 | 2.459302 | 1.625835 |
| **Left anterior insula** | 2.006323 | 2.327827 | 2.087493 |
| **Left posterior insula** | 1.969881 | 2.383903 | 1.650281 |
| **Right cuneus** | 1.969836 | 2.454178 | 2.713713 |
| **Right middle cingulate gyrus** | 1.959969 | 2.432305 | 2.841076 |
| **Right Cerebellum White Matter** | 1.940778 | 2.233227 | 3.350152 |
| **Right superior occipital gyrus** | 1.933231 | 2.477784 | 2.178569 |
| **Left frontal pole** | 1.898032 | 2.350276 | 1.933106 |
| **Left parietal operculum** | 1.888417 | 2.232415 | 2.179631 |
| **Right triangular part of the inferior frontal gyrus** | 1.879409 | 2.056128 | 3.623433 |
| **Right parietal operculum** | 1.876598 | 2.103572 | 3.654405 |
| **Right occipital pole** | 1.844531 | 2.420899 | 1.864237 |
| **Right postcentral gyrus** | 1.73389 | 1.963897 | 2.216223 |
| **Right parahippocampal gyrus** | 1.700616 | 1.806945 | 3.299364 |
| **Left middle cingulate gyrus** | 1.677947 | 2.023637 | 1.93905 |
| **Right middle frontal gyrus** | 1.640473 | 1.956614 | 2.733248 |
| **Left Cerebellum White Matter** | 1.634217 | 1.886694 | 1.994007 |
| **Left occipital pole** | 1.607958 | 2.10123 | 1.710682 |
| **Right opercular part of the inferior frontal gyrus** | 1.606704 | 1.862707 | 2.983784 |
| **Right anterior insula** | 1.576673 | 1.83106 | 2.568844 |
| **Right precentral gyrus** | 1.56827 | 1.689601 | 3.136704 |
| **Right Pallidum** | 1.561033 | 1.345314 | 3.970727 |
| **Left supplementary motor cortex** | 1.54779 | 2.018619 | 1.426876 |
| **Left parahippocampal gyrus** | 1.543659 | 1.952332 | 1.641477 |
| **Left middle temporal gyrus** | 1.536823 | 2.045607 | 0.792286 |
| **Right superior parietal lobule** | 1.525395 | 1.816316 | 2.255325 |
| **Left supramarginal gyrus** | 1.506635 | 1.782195 | 1.618199 |
| **Right fusiform gyrus** | 1.505367 | 1.383632 | 3.901395 |
| **Right occipital fusiform gyrus** | 1.500766 | 1.98387 | 1.366842 |
| **Left superior temporal gyrus** | 1.466682 | 1.931225 | 1.548261 |
| **Right Cerebral White Matter** | 1.46494 | 1.532713 | 3.080928 |
| **Left occipital fusiform gyrus** | 1.448692 | 1.774211 | 1.510537 |
| **Left cuneus** | 1.446867 | 1.75561 | 1.556874 |
| **Left triangular part of the inferior frontal gyrus** | 1.434262 | 1.494599 | 1.698296 |
| **Left posterior orbital gyrus** | 1.431487 | 1.884696 | 1.344898 |
| **Right supramarginal gyrus** | 1.426303 | 1.559537 | 2.853231 |
| **Left middle frontal gyrus** | 1.426016 | 1.832797 | 1.336133 |
| **Right inferior occipital gyrus** | 1.425688 | 1.509505 | 3.069728 |
| **Right Putamen** | 1.418899 | 1.604831 | 2.67385 |
| **Right precuneus** | 1.392701 | 1.700503 | 2.127553 |
| **Right superior temporal gyrus** | 1.377205 | 1.64672 | 2.072957 |
| **Left postcentral gyrus** | 1.372136 | 1.614628 | 1.427209 |
| **Right lateral orbital gyrus** | 1.35255 | 1.306483 | 3.39629 |
| **Right angular gyrus** | 1.349828 | 1.415976 | 2.841785 |
| **Right superior frontal gyrus medial segment** | 1.333963 | 1.622221 | 2.220998 |
| **Right frontal pole** | 1.328509 | 1.913694 | 0.993688 |
| **Right posterior cingulate gyrus** | 1.325541 | 1.317757 | 3.257024 |
| **Left precuneus** | 1.323096 | 1.722416 | 1.350707 |
| **Left opercular part of the inferior frontal gyrus** | 1.311485 | 1.517892 | 1.710904 |
| **Right central operculum** | 1.309482 | 1.284356 | 3.291515 |
| **Left transverse temporal gyrus** | 1.307912 | 1.712096 | 1.147481 |
| **Right Amygdala** | 1.305618 | 1.684723 | 1.166361 |
| **Right precentral gyrus medial segment** | 1.284506 | 1.391357 | 2.597862 |
| **Left calcarine cortex** | 1.28335 | 1.592959 | 1.715128 |
| **Left middle occipital gyrus** | 1.280566 | 1.42371 | 1.755972 |
| **Right posterior orbital gyrus** | 1.274695 | 1.612437 | 1.848147 |
| **Left Thalamus Proper** | 1.258116 | 1.317389 | 1.778195 |
| **Right Basal Forebrain** | 1.255854 | 1.674078 | 1.401289 |
| **Left Amygdala** | 1.241828 | 1.623001 | 1.052247 |
| **Right entorhinal area** | 1.235723 | 1.516338 | 2.01662 |
| **Right posterior insula** | 1.22059 | 1.293435 | 2.370574 |
| **Right medial orbital gyrus** | 1.205013 | 1.636646 | 1.261296 |
| **Left medial orbital gyrus** | 1.203049 | 1.763435 | 0.615294 |
| **Left angular gyrus** | 1.199965 | 1.440503 | 1.736412 |
| **Right supplementary motor cortex** | 1.191615 | 1.498562 | 1.509932 |
| **Right postcentral gyrus medial segment** | 1.18708 | 1.183282 | 2.816602 |
| **Left Basal Forebrain** | 1.172546 | 1.256472 | 2.13287 |
| **Right Caudate** | 1.162546 | 1.421159 | 1.524807 |
| **Left precentral gyrus** | 1.149604 | 1.444933 | 1.642663 |
| **Left lingual gyrus** | 1.133895 | 1.280783 | 1.0391 |
| **Right Thalamus Proper** | 1.130971 | 1.166331 | 2.310839 |
| **Left anterior orbital gyrus** | 1.124849 | 1.138302 | 1.085802 |
| **Cerebellar Vermal Lobules VIII-X** | 1.111519 | 1.261751 | 1.777773 |
| **Left precentral gyrus medial segment** | 1.107725 | 1.331356 | 1.570372 |
| **Left superior occipital gyrus** | 1.09812 | 1.330437 | 1.328637 |
| **Right calcarine cortex** | 1.063215 | 1.104938 | 2.266497 |
| **Left superior frontal gyrus medial segment** | 1.051185 | 1.311405 | 0.98221 |
| **Left central operculum** | 1.042423 | 1.28905 | 1.677264 |
| **Right temporal pole** | 1.041058 | 1.020346 | 2.35263 |
| **Right medial frontal cortex** | 1.035035 | 1.508816 | 0.634171 |
| **Right anterior cingulate gyrus** | 1.031524 | 1.184972 | 1.667439 |
| **Right subcallosal area** | 1.029382 | 0.987824 | 2.726627 |
| **Right middle temporal gyrus** | 1.010227 | 1.35277 | 1.051329 |
| **Right anterior orbital gyrus** | 1.006343 | 1.203667 | 1.13872 |
| **Left temporal pole** | 1.004586 | 0.940446 | 1.878683 |
| **Left Accumbens Area** | 0.974294 | 0.834598 | 2.707159 |
| **Right middle occipital gyrus** | 0.961899 | 1.103044 | 1.700676 |
| **Left Pallidum** | 0.96069 | 1.089665 | 1.652462 |
| **Left frontal operculum** | 0.958735 | 1.234722 | 0.798594 |
| **Right lingual gyrus** | 0.917128 | 0.987942 | 1.48752 |
| **Left inferior occipital gyrus** | 0.910536 | 1.134497 | 1.447446 |
| **Left planum temporale** | 0.90719 | 1.071082 | 0.915568 |
| **Left posterior cingulate gyrus** | 0.901592 | 0.992121 | 1.082107 |
| **Cerebellar Vermal Lobules VI-VII** | 0.894504 | 1.023508 | 1.696253 |
| **Left medial frontal cortex** | 0.890612 | 1.277378 | 0.655267 |
| **Left Caudate** | 0.876901 | 0.874921 | 1.94564 |
| **Right frontal operculum** | 0.872798 | 0.80191 | 1.956279 |
| **Left inferior temporal gyrus** | 0.857028 | 0.935976 | 1.408253 |
| **Left Cerebellum Exterior** | 0.846625 | 0.889021 | 1.523993 |
| **Right Accumbens Area** | 0.845867 | 0.948042 | 1.182625 |
| **Left lateral orbital gyrus** | 0.82477 | 0.733449 | 2.305545 |
| **Left postcentral gyrus medial segment** | 0.811194 | 1.010706 | 1.089935 |
| **Right planum temporale** | 0.784989 | 0.927357 | 0.902161 |
| **Left Ventral DC** | 0.774954 | 0.882938 | 1.07639 |
| **Right Hippocampus** | 0.758967 | 0.761128 | 2.022766 |
| **Left entorhinal area** | 0.731572 | 0.853865 | 0.908468 |
| **Right Cerebellum Exterior** | 0.723832 | 0.67137 | 1.955849 |
| **Left subcallosal area** | 0.71836 | 0.678074 | 1.256032 |
| **Right gyrus rectus** | 0.710091 | 0.84026 | 1.182328 |
| **Right Ventral DC** | 0.693764 | 0.682799 | 1.699471 |
| **Right transverse temporal gyrus** | 0.647428 | 0.801876 | 0.966188 |
| **Left gyrus rectus** | 0.645669 | 0.869991 | 0.717333 |
| **Left superior frontal gyrus** | 0.642327 | 0.71801 | 0.636798 |
| **Left anterior cingulate gyrus** | 0.628465 | 0.705453 | 0.965663 |
| **Left Hippocampus** | 0.623639 | 0.721379 | 1.011275 |
| **Brain Stem** | 0.600897 | 0.594921 | 1.403171 |
| **Left fusiform gyrus** | 0.502977 | 0.583696 | 0.611204 |
| **Left orbital part of the inferior frontal gyrus** | 0.500957 | 0.669735 | 0.657271 |
| **Cerebellar Vermal Lobules I-V** | 0.456003 | 0.484387 | 0.743909 |
| **Right superior frontal gyrus** | 0.352499 | 0.483553 | 0.470705 |
| **Right orbital part of the inferior frontal gyrus** | 0.196086 | 0.348605 | 0.57359 |

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