Multimodal imaging for enhanced assessment of neurological diseases associated with brain lesions

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Ph.D. Thesis

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ABBREVIATIONS

ADC: apparent diffusion coefficient

AMT: alpha-[^{11}C]-methyl-L-tryptophan

BDI-II: Beck Depression Inventory-II

CNS: central nervous system

Cr: creatine

CT: computer tomography

DWI: diffusion-weighted imaging

[^{18}F]-FDG: 2-deoxy-2-[^{18}F]fluoro-D-glucose

[^{18}F]-FET: O-(2-[^{18}F]fluoroethyl)-L-tyrosine

FLAIR: fluid-attenuated inversion recovery

IDH1: isocitrate-dehydrogenase 1

IDO1: indoleamine-2,3-dioxygenase 1

KPS: Karnofsky performance status

LAT1: L-type amino acid transporter 1

MDD: major depressive disorder

MGMT: O^6-methylguanine-DNA methyltransferase

mI: myo-inositol

MRI: magnetic resonance imaging

MRS: magnetic resonance spectroscopy

MS: multiple sclerosis

NAA: N-acetyl-aspartate

NAWM: normal-appearing white matter

PET: positron emission tomography

PWI: perfusion-weighted imaging

rCBV: relative cerebral blood volume

T/N ratio: tumor/contralateral normal ratio

T1-Gad: T1-weighted gadolinium-enhanced

WMHs: white matter hyperintensities

WMLs: white matter lesions

I. INTRODUCTION

Multimodal imaging, representing the summation of information from different neuroimaging modalities, has advanced rapidly in the last decades. The better access to advanced magnetic resonance imaging (MRI) or even hybrid devices, e.g., positron emission tomography (PET)/computer tomography (CT) and PET/MRI has facilitated this process, as well as the increasing recognition of the clinical benefits of multimodal data.

Advanced MRI techniques, including diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and magnetic resonance spectroscopy (MRS) can provide additional, measurable diagnostic information beside the conventional, structural MRIs. DWI may assess tissue cellularity by measuring the apparent diffusion coefficient (ADC), therefore it can assess tumor cellularity, peritumoral edema, regions of tumor hypoxia, integrity of white matter tracts, and postoperative injury. Dynamic susceptibility contrast, one of the currently employed PWI techniques, can estimate angiogenesis via relative cerebral blood volume (rCBV). rCBV may be elevated in tumors and decreased in non-tumorous lesions such as demyelination. MRS may give information about the concentration of major neurotransmitters and metabolites, such as choline, lactate, creatine (Cr), myo-inositol (mI), N-acetyl-aspartate (NAA), thus helping to understand the underlying structure of interrogated brain tissue.

Besides MRI techniques, PET imaging can detect and characterize different types of lesions based on their metabolic properties, such as altered glucose, nucleoside, and amino acid metabolism. 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]-FDG)-PET is the most commonly used PET radiotracer in neuroradiology. It may delineate epileptic lesions and perilesional functional abnormalities, differentiate dementias or malignant from benign lesions, and distinguish recurrent tumors from radiation injury. The value of radiolabeled amino acids, especially tryptophan derivatives, as potential imaging probes to visualize organs and tumors, has been long recognized and has emerged as a useful supplementary imaging tool in tumor imaging. Currently, the most commonly used amino acid tracers are L-methyl-[^{11}C]-methionine, O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]-FET), [^{18}F]fluoro-deoxy-phenylalanine, and alpha-[^{11}C]-methyl-L-tryptophan (AMT). Amino acid PET imaging can detect interictal or peri-ictal cortical increased uptake (as compared to non-epileptic cortex) associated with tumor-associated epilepsy, and it can also differentiate tumor tissue from non-tumoral lesions.

The above-mentioned imaging techniques may provide detailed, objective, quantitative, thus comparable data from several neurological diseases; therefore, multimodal imaging can facilitate the accurate differential diagnosis, the more specific treatment and prognosis not only in diseases with visible lesions (e.g., brain tumors, migraine, multiple sclerosis [MS]), but also in conditions with microstructural or metabolic changes invisible on conventional MRI (e.g., dementia, depression).

In the present work, we focused on three different neurological diseases associated with detectable brain lesions (brain tumors, migraine, and MS) and investigated them using multimodal imaging techniques, including advanced MRI (DWI, PWI, MRS) and PET studies.

I.1. Brain tumors

Malignant brain and other central nervous system (CNS) tumors account for approximately 1% of all invasive cancer cases, but they are the most commonly diagnosed solid tumors in children and adolescents and the leading cause of cancer death among males aged <40 years and females aged <20 years. Based on a population-based data analysis from the Central Brain Tumor Registry of the United States, malignant tumors account for less than one-third of all brain and other CNS tumors but the majority of deaths from the disease; among them diffuse gliomas, and within those glioblastomas (49%), are the most common. Although gliomas may occur throughout the whole CNS, diffuse gliomas are mostly detected in the supratentorial region of the brain, especially in adults. There are few established risk factors, such as ionizing radiation and genetic predisposition, although a hereditary component was noted only for a small portion of brain tumors. Five-year relative survival for all malignant brain tumors combined increased between 1975 to 1977 and 2009 to 2015 from 23% to 36%, while 5-year glioblastoma survival only increased from 4% to 7% during the same time period. Clinical prognostic factors for glioblastoma include age, performance status, tumor radiologic features, and extent of initial tumor resection. Among molecular features, high Ki-67 nuclear labeling index carries unfavorable prognosis, whereas isocitrate dehydrogenase 1 (IDH1) mutation is associated with prolonged survival.

The classification of gliomas has had several modifications in recent years in parallel with growing molecular understanding and progress in detection and diagnosis. This process has led to the recent World Health Organization classification, which incorporated molecular markers into the nomenclature to better reflect clinical characteristics and prognosis; e.g., the distinction for several subtypes is currently determined by the presence of mutations in the IDH-1/IDH-2 genes and 1p/19q codeletion.

In general, the most common clinical manifestation of brain tumors are seizures, focal neurological deficit, cognitive impairment, but patients with brain tumors have an increased risk for depressive symptoms as well. A recent review found a pooled depression prevalence of 21.7% in brain tumor patients. While most previous studies found no clear association between brain tumor-related depression and clinical variables, including gender, functional status, tumor size, lobe, laterality, or treatment approaches, depression was associated with reduced physical function, cognitive impairment, and impaired quality of life. Moreover, in patients with high-grade glioma, depression was associated with shorter survival. Tumor-associated depressive symptoms may be related to overlapping molecular mechanisms involved in tumor pathology and depression.

The diagnosis, treatment planning, and follow-up of glioblastomas are mostly based on *conventional MRI* characteristics, including T1-weighted gadolinium-enhanced (T1-Gad), T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences. The contrast-enhancing tumor mass is the primary target of glioblastoma treatment, including resective surgery and fractionated radiotherapy. However, glioblastomas are highly infiltrative tumors with malignant cells extending well beyond the contrast-enhancing tumor mass. Glioma-infiltrated non-enhancing regions commonly show high signal intensity on T2/FLAIR sequences but cannot be differentiated accurately from pure vasogenic edema that shows similar signal changes on MRI. Therefore, non-enhancing glioblastoma-infiltrated regions are difficult to detect, and they may be undertreated. On post-treatment MRI, progressive contrast enhancement can indicate glioblastoma progression or radiation injury, but these two pathologies (which can also coexist) are difficult to differentiate by conventional MRI which is recommended by the Response Assessment in Neuro-Oncology Working Group.

Among *advanced MRI techniques*, DWI can differentiate tumor infiltration from vasogenic edema both manifesting as hyperintense regions on FLAIR images based on cellularity; while PWI can help distinguish radiation necrosis from true tumor recurrence (showing high vascularization and increased blood brain barrier permeability) in post-treatment patients both displaying gadolinium enhancement on T1-Gad images.

Amino acid PET is increasingly used in the evaluation of newly-diagnosed and recurrent gliomas; it has been accurate to distinguish tumor tissue from normal brain and non-tumoral lesions, as well as to detect glioma-infiltrated brain beyond the MRI contrast-enhancing regions. The presence of glioma cells in these non-enhancing infiltrative glioma portions showing increased amino acid uptake on PET has been demonstrated in stereotactically obtained surgical tissue samples. Furthermore, amino acid PET features may also have prognostic value. For example, a [^{18}F]-FET-PET study showed that the PET-defined biological tumor volume in newly-diagnosed glioblastomas was a prognostic imaging biomarker for survival, independent of O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status.

Commonly used amino acid PET tracers, including AMT used in the present studies, share transport mechanisms via the L-type amino acid transporter-1 (LAT1), which is upregulated in malignant gliomas. Tumoral AMT accumulation is also facilitated by metabolism via the immunosuppressive kynurenine pathway, whose upregulation contributes to tumor progression and poor survival. Immune-mediated activation of indoleamine-2,3-dioxygenase 1 (IDO1), a key enzyme of the immunosuppressive kynurenine pathway, and increased metabolism via the 3-hydroxykynurenine branch of the pathway can lead to elevated levels of the neurotoxic quinolinic acid. This has been associated with major depressive disorder (MDD) and suicidality and implicated in intervening pathomechanisms of systemic inflammation, cancer, and depressive symptoms. AMT-PET studies in patients with MDD or a history of suicide attempts found focal abnormalities in the fronto-limbic structures, mostly in cingulate and frontal/prefrontal cortex, indicating abnormal serotonergic activity in these regions. Our

previous studies also showed abnormal AMT uptake and kinetic variables not only in brain tumors, where its values correlated with key enzymes of the kynurenine pathway in resected tumor samples, but also in the contralateral non-tumoral hemisphere. Moreover, high uptake in the thalamus was associated with shorter survival in post-treatment gliomas. In a preliminary study, tryptophan transport and metabolic rates in the non-tumoral thalamus, striatum, and frontal cortex, measured by AMT-PET, were associated with depression in patients with brain tumors.

I.2. Multiple sclerosis and migraine

Multiple sclerosis is one of the most common immune-mediated CNS disorders causing demyelination, inflammation, gliosis, and neuronal loss disseminated in different areas of the CNS and occurring at different times. White matter lesions (WMLs) in MS are typically situated in the juxtacortical, cortical, periventricular, pericallosal, callosal, infratentorial, and spinal cord regions. Moreover, contrast-enhancing lesions can also be observed in the active phase, while lesions with severe axonal damage or glial necrosis can be seen as a hypointense region on T1-weighted images.

Migraine is a neurological disease characterized by recurrent headache attacks associated with temporary symptoms of autonomic nervous system dysfunction and accompanied by focal auras in some cases. Migraine patients have an increased risk of developing supratentorial deep WMLs, or silent posterior ischemic infarcts. Migraine-related WMLs are small, ovoid lesions mostly found in periventricular and deep brain white matter sparing the juxtacortical region. However, in some cases, WMLs in migraine may also be in typical MS areas, such as juxtacortical or callosal regions, and at least 24.4% of headache patients may fulfill the radiological diagnostic (McDonald) criteria of MS. In addition, the high co-morbidity between MS and migraine is well known.

Despite the advances in neuroimaging techniques, differentiation of the WMLs of these two pathologies remains difficult. A recent review summarizing MRS studies in migraine patients concluded that the published data support the hypothesis of impaired energetics and mitochondrial dysfunction in migraine showing decreased NAA and increased lactate levels. On the other hand, decreased NAA in MS lesions is a commonly reported abnormality among elevated choline and mI levels. However, only a few studies compared WMLs of migraine and MS patients, and the data are mostly confined to DWI where the mean ADC values in frontal, fronto-parietal and temporal normal-appearing white matter (NAWM) were significantly higher in the MS group than in subjects with white matter hyperintensities (WMHs) and the control group. On the other hand, our recent study concluded that an accurate differential diagnosis of WMLs by conventional MRI was probably not possible in individual patients.

II. OBJECTIVES

Our overall aim was to evaluate advanced non-invasive imaging techniques, which can provide additional information about different neurologic diseases, associated with brain

lesions, as compared to conventional radiological studies; thus helping the diagnosis, treatment-planning and follow-up of patients with brain tumors, migraine, or multiple sclerosis.

In *Study 1*, we utilized MRI with DWI and AMT-PET to identify metabolic heterogeneity within the contrast-enhancing tumor mass of glioblastomas, while we also compared the amino acid uptake and cellularity in different glioblastoma subregions. In addition, we evaluated the potential prognostic value of ADC and AMT uptake in these imaging defined tumor subregions while taking other prognostic clinical, histologic, molecular, and imaging characteristics into consideration.

In *Study 2*, we evaluated how well rCBV obtained from PWI can identify non-enhancing tumor-infiltrated regions defined by AMT-PET, and we tested this in both newly-diagnosed and recurrent glioblastomas. We investigated whether low rCBV values in non-enhancing tumor regions can predict low amino acid uptake indicating the lack of robust tumor infiltration in the area.

In *Study 3*, we examined the relation of clinical and tumor characteristics to depression scores in patients with newly-diagnosed and recurrent primary brain tumors. In addition, we evaluated regional cortical and subcortical tryptophan metabolism using AMT-PET as a potential imaging marker of tumor-associated depression and tested if the imaging variables are specific for any of the three major aspects of depression (somatic, affective, cognitive). Finally, we assessed if Beck Depression Inventory-II (BDI-II) scores are associated with variations in plasma tryptophan metabolites in this patient group.

In *Study 4*, our aim was to investigate WMLs in patients with migraine and multiple sclerosis using advanced MRI techniques, such as single proton MRS, PWI, and DWI. In addition, we compared the findings to a control group to define the differences between the two diseases.

III. SUMMARY OF STUDIES

Our multimodal imaging studies included groups of adult patients with primary brain tumors (Studies 1, 2, 3) and patients with migraine or MS (Study 4). The first three studies were approved by the Institutional Review Board of Wayne State University (Detroit, Michigan, USA). The fourth study was approved by the Regional Research Ethics Committee of the Clinical Center of University of Pécs. Written informed consent was obtained from all participants. In all studies, the statistical analysis was carried out using

IBM SPSS Statistics version 24.0 (Studies 1-3) or version 25.0 (Study 4). A p-value of <0.05 was considered to be significant.

III.1. Multimodal imaging-defined subregions in newly-diagnosed glioblastoma: impact on overall survival (John et al. Neuro-Oncol, 2019)

III.1.1. *Purpose of the study:* Although glioblastomas are heterogeneous brain-infiltrating tumors, their treatment is mostly focused on the contrast-enhancing tumor mass. In this study, we combined conventional MRI, DWI, and AMT-PET to explore imaging-defined glioblastoma subregions and evaluate their potential prognostic value.

III.1.2. *Subjects and Methods:* Contrast-enhanced T1, T2/FLAIR MR images, ADC maps from DWI, and AMT-PET images were analyzed in 30 patients with newly-diagnosed glioblastoma. Five tumor subregions were identified based on a combination of MRI contrast enhancement, T2/FLAIR signal abnormalities, and AMT uptake on PET. ADC and AMT uptake tumor/contralateral normal cortex (T/N) ratios in these tumor subregions were correlated, and their prognostic value was determined.

III.1.3. *Results:* A total of 115 MRI/PET-defined subregions were analyzed. Most tumors showed not only a high-AMT uptake (T/N ratio > 1.65, N = 27) but also a low-uptake subregion (N = 21) within the contrast-enhancing tumor mass. High AMT uptake extending beyond contrast enhancement was also common (N = 25) and was associated with low ADC (r = -0.40, p = 0.05). High AMT uptake (exceeding a 2.38 T/N ratio threshold) in the contrast-enhancing tumor subregions was strongly prognostic for overall survival (hazard ratio: 7.83; 95% CI: 1.98-31.02, p = 0.003), independent of clinical and molecular genetic prognostic variables. Non-resected high-AMT uptake subregions predicted the sites of tumor progression on post-treatment PET performed in 10 patients.

III.1.4. *Conclusions:* Glioblastomas show heterogeneous amino acid uptake with high-uptake regions often extending into non-enhancing brain with high cellularity; non-resection of these predict the site of post-treatment progression. High tryptophan uptake values in MRI contrast-enhancing tumor subregions are a strong, independent imaging marker for longer overall survival.

III.2. Multimodal imaging of non-enhancing glioblastoma regions (John et al. Mol Imaging, 2019)

III.2.1. *Purpose of the study:* Clinical glioblastoma treatment mostly focuses on the contrast-enhancing tumor mass. Amino acid PET can detect additional, non-enhancing glioblastoma-infiltrated brain regions that are difficult to distinguish on conventional MRI. We combined MRI with PWI and amino acid PET to evaluate such non-enhancing glioblastoma regions.

III.2.2. *Subjects and Methods:* Structural MRI, rCBV maps from PWI, and AMT-PET images were analyzed in 20 patients with glioblastoma. The AMT uptake and rCBV

(expressed as T/N ratios) were compared in non-enhancing tumor portions showing increased signal on T2/FLAIR images.

III.2.3. *Results:* Thirteen (65%) tumors showed robust heterogeneity in non-enhancing T2/FLAIR hyperintense areas on AMT-PET, whereas the non-enhancing regions in the remaining 7 cases had homogeneous AMT uptake (low in 6, high in 1). AMT and rCBV T/N ratios showed only a moderate correlation in the non-enhancing regions ($r = 0.41$, $p = 0.017$), but regions with very low rCBV (<0.79 T/N ratio) had invariably low AMT uptake.

III.2.4. *Conclusions:* The findings demonstrate the metabolic and perfusion heterogeneity of non-enhancing T2/FLAIR hyperintense glioblastoma regions. Amino acid PET imaging of such regions can detect glioma-infiltrated brain for treatment targeting; however, very low rCBV values outside the contrast-enhancing tumor mass make increased AMT uptake in non-enhancing glioblastoma regions unlikely.

III.3. Depression and tryptophan metabolism in patients with primary brain tumors: Clinical and molecular imaging correlates (John et al. Brain Imaging Behav. 2021)

III.3.1. *Purpose of the study:* Patients with brain tumors have an increased risk for depression, whose underlying pathomechanism may involve dysregulated tryptophan/kynurenine metabolism. In this study, we analyzed the relation of depressive symptoms to clinical and tumor characteristics as well as cerebral and systemic tryptophan metabolism in patients with primary brain tumors.

III.3.2. *Subjects and Methods:* Sixty patients with newly-diagnosed or recurrent primary brain tumor underwent testing with the BDI-II, and 34 patients also had AMT-PET imaging. BDI-II scores were correlated with clinical and tumor-related variables, cerebral regional AMT metabolism measured in the non-tumoral hemisphere, and plasma tryptophan metabolite levels.

III.3.3. *Results:* Sixteen patients (27%) had BDI-II scores indicating depression, including 6 with moderate/severe depression. High BDI-II scores were independent of clinical and tumor-related variables except lower Karnofsky Performance Status (KPS) scores. In patients with recurrent malignant gliomas, depression was associated with shorter survival (hazard ratio: 3.7; $p = 0.048$). High BDI-II total and somatic subscale scores were associated with higher frontal cortical and thalamic AMT metabolic values measured on PET. In contrast, plasma tryptophan and kynurenine metabolite levels did not correlate with the BDI-II scores.

III.3.4. *Conclusions:* In conclusion, our results confirm previous data that depression affects more than ¼ of patients with primary brain tumors, it is largely independent of tumor characteristics and is associated with shorter survival in patients with recurrent malignant gliomas. On PET imaging, higher tryptophan metabolism in the frontal cortex and thalamus was found in those with brain tumor-associated depression and supports the role of dysregulated tryptophan/kynurenine metabolism in this condition.

III.4. Differentiation of hemispheric white matter lesions in migraine and multiple sclerosis with similar radiological features using advanced MRI (John et al., Front Neurosci, 2024)

III.4.1. *Purpose of the study:* White matter hyperintensities, presented on T2-weighted or FLAIR MRI sequences, are lesions in the human brain that can be observed in both migraine and multiple sclerosis.

III.4.2. *Subjects and Methods:* Seventeen migraine patients and 15 patients with relapsing-remitting multiple sclerosis with WMHs, and 17 healthy subjects age- and sex-matched to the migraine group were prospectively enrolled and underwent conventional and advanced MRI studies with DWI and PWI, and single voxel proton MRS.

III.4.3. *Results:* In both patient groups, elevated T2 relaxation time, ADC values, and decreased NAA levels were found in the intralesional white matter compared to the contralateral NAWM, while there was no difference between the hemispheres of the control subjects. Migraine patients had the lowest intralesional Cr and mI values among the three groups, while patients with MS showed the highest intralesional T1 and T2 relaxation times, ADC, and mI values. In the contralateral NAWM, the same trend with mI changes was observed in migraineurs and MS patients. No differences in perfusion variables were observed in any groups.

III.4.4. *Conclusions:* Our multimodal study showed that tissue damage is detectable in both diseases. Despite some differences in various advanced MRI measures, with more severe injury detected in MS lesions, we could not clearly differentiate the two white matter lesion types.

IV. SUMMARY

New findings:

- Amino acid uptake can differentiate metabolically active glioblastoma subregions (often showing dense cellularity) from necrotic or edematous areas, in both enhancing and non-enhancing areas within the tumor.
- There was a correlation between the ADC and AMT uptake ratios in the whole set of tumor subregions driven by the non-enhancing, high-AMT tumor subregions, indicating tumor-infiltrated brain, and by the non-enhancing, T2/FLAIR hyperintense area with low-AMT uptake, consistent with peritumoral vasogenic edema.
- High tryptophan uptake in MRI contrast-enhancing tumor subregions appears to be a strong, independent imaging biomarker for longer survival in patients with newly-diagnosed glioblastomas.
- AMT-PET can detect both tumor-infiltrated and vasogenic edema in the majority of the tumors, but the uptake values showed only weak associations with rCBV measured in the same regions. However, areas with very low rCBV were

invariably associated with low tryptophan uptake, indicative of vasogenic edema rather than active infiltrating tumor.

- There were no significant associations between BDI-II depression scores and clinical or tumor-related variables except KPS scores in patients with primary brain tumor.
- Higher BDI-II scores were associated with higher frontal cortical and thalamic (and, to a lesser degree, temporal cortical) AMT K values measured by PET imaging in the non-tumor-affected hemisphere, suggesting that dysregulated tryptophan metabolism in these regions may play a role in tumor-associated depression.
- No association was found between depression and plasma tryptophan and kynurenine metabolite levels.
- Elevated T2 relaxation time, ADC values, and decreased NAA values were found in the intralesional white matter compared to the contralateral NAWM in patients with migraine and MS, while there was no difference between the hemispheres in the control subjects.
- Migraine patients had the lowest intralesional Cr and mI values among the three groups, while patients with MS showed the highest intralesional T1, T2 relaxation times, ADC, and mI values. In the contralateral NAWM, the same trend of mI changes was observed both in migraineurs and MS patients.

My studies were based on the previous notions that combination of conventional MRI with advanced imaging techniques may offer additional information in imaging of different neurological diseases. The four studies summarized above emphasized the value of multimodal imaging, such as MRI combined with amino acid PET or MRS techniques, which may provide more accurate and quantitative information in diagnosis and differentiation of different neurological diseases, including brain tumors, migraine, and multiple sclerosis. Three of the above-mentioned studies showed the usefulness of the AMT-PET in brain tumor imaging, as it could accurately capture glioblastoma heterogeneity and differentiate metabolically active tumor subregions in enhancing and non-enhancing areas. Moreover, the results demonstrated the prognostic value of tryptophan uptake in patients with newly-diagnosed and recurrent brain tumors, and also its connection with tumor-related depression which can help better understand the underlying mechanism and evaluate pharmacologic interventions targeting the dysregulated kynurenine pathway. Although these data are encouraging, the clinical use of AMT is limited due to the short half-life of ^{11}C (~20 min) and the cumbersome radiosynthesis of AMT. Our research team has constantly sought the possibility to develop newer, clinically more feasible, [^{18}F]-labeled tryptophan analog tracers in order to overcome these limitations. After reviewing preclinical studies with newly-developed [^{18}F]-labeled tryptophan analogs, 1-(2-^{18}F-fluoroethyl)-L-tryptophan emerged a promising candidate for human studies, as it showed metabolism via the kynurenine pathway and showed robust uptake in patient-derived xenograft models. A recent pilot

study verified its strong potential for clinical brain tumor imaging. Further studies may extend our initial results to a larger group, thus helping to improve pre- and post-treatment evaluation of brain tumors. Although the fourth study found several differences in the imaging markers of WMLs in migraine and MS patients, a clear differentiation could not be obtained. Further studies may investigate the reported differences in a larger sample, which may even lead to a threshold helping to distinguish the two diseases from each other in the near future.

V. PUBLICATIONS

V.1. Full-length, peer-reviewed publications related to this thesis

1. **John F**, Bosnyák E, Robinette NL, Amit-Yousif AJ, Barger GR, Shah KD, Michelhaugh SK, Klinger NV, Mittal S, Juhász C. Multimodal imaging-defined subregions in newly-diagnosed glioblastoma: Impact on overall survival. Neuro Oncol. 2019 Feb 14;21(2):264-273. doi: 10.1093/neuonc/noy169. PMID: 30346623; PMCID: PMC6374760. (**IF: 10,247**)
2. **John F**, Robinette NL, Amit-Yousif AJ, Bosnyák E, Barger GR, Shah KD, Mittal S, Juhász C. Multimodal imaging of non-enhancing glioblastoma regions. Mol Imaging. 2019 Jan-Dec;18:1536012119885222. doi: 10.1177/1536012119885222. PMID: 31736437; PMCID: PMC6862774. (**IF: 2,763**)
3. **John F**, Michelhaugh SK, Barger GR, Mittal S, Juhász C. Depression and tryptophan metabolism in patients with primary brain tumors: Clinical and molecular imaging correlates. Brain Imaging Behav. 2021 Apr;15(2):974-985. doi: 10.1007/s11682-020-00305-7. PMID: 32767048; PMCID: PMC7865029. (**IF: 3,978**)
4. Bonomi R, **John F**, Patel S, Barger G, Robinette N, Amit-Yousif AJ, Dominello M, Juhász C. Multimodal neuroimaging of gliomatosis cerebri: A case series of four patients. Acta Radiol Open. 2020 Aug 21;9(8):2058460120942789. doi: 10.1177/2058460120942789. PMID: 32913666; PMCID: PMC7444143.
5. **John F**, Muzik O, Mittal S, Juhász C. Fluorine-18-labeled PET radiotracers for imaging tryptophan uptake and metabolism: A systematic review. Mol Imaging Biol. 2020 Aug;22(4):805-819. doi: 10.1007/s11307-019-01430-6. PMID: 31512038; PMCID: PMC7064410. (**IF: 3,488**)
6. **John F,** Kis-Jakab G, Komáromy H, Perlaki G, Orsi G, Bosnyák E, Rozgonyi R, Trauninger A, Eklics K, Kamson DO, Pfund Z. Differentiation of hemispheric white matter lesions in migraine and multiple sclerosis with similar radiological features using advanced MRI. Front Neurosci. 2024 May 9;18:1384073. doi: 10.3389/fnins.2024.1384073. PMID: 38784095; PMCID: PMC11112078. (**IF: 4,3***)

V.2. Publications not related to this thesis

1. He M, Kis-Jakab G, Komáromy H, Perlaki G, Orsi G, Bosnyák E, Rozgonyi R, **John F**, Trauninger A, Eklics K, Pfund Z. Volumetric alteration of brainstem in female migraineurs with and without aura. Clin Neurol Neurosurg. 2024 Jan;236:108089. doi: 10.1016/j.clineuro.2023.108089. Epub 2023 Dec 19. PMID: 38141551. (**IF: 1,9**)
2. He M, Kis-Jakab G, Komáromy H, Perlaki G, Orsi G, Bosnyák E, Rozgonyi R, **John F**, Trauninger A, Eklics K, Pfund Z. The volume of the thalamus and hippocampus in a right-handed female episodic migraine group. Front Neurol.

2023 Oct 19;14:1254628. doi: 10.3389/fneur.2023.1254628. PMID: 37928149; PMCID: PMC10622660. (**IF: 3,4**)

3. Juhász C, **John F**. Utility of MRI, PET, and ictal SPECT in presurgical evaluation of non-lesional pediatric epilepsy. Seizure. 2020 Apr;77:15-28. doi: 10.1016/j.seizure.2019.05.008. Epub 2019 May 11. PMID: 31122814; PMCID: PMC6842677. (**IF: 3,184**)
4. Jeong JW, Lee MH, **John F**, Robinette NL, Amit-Yousif AJ, Barger GR, Mittal S, Juhász C. Feasibility of multimodal MRI-based deep learning prediction of high amino acid uptake regions and survival in patients with glioblastoma. Front Neurol. 2019 Dec 17;10:1305. doi: 10.3389/fneur.2019.01305. PMID: 31920928; PMCID: PMC6928045. (**IF: 2,889**)
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7. Darnai G, Nagy SA, Horváth R, Ács P, Perlaki G, Orsi G, Kovács N, Altbäcker A, Plózer E, Tényi D, Weintraut R, Schwarcz A, **John F**, Varga E, Bereczkei T, Clemens Z, Komoly S, Janszky J. Iron concentration in deep gray matter structures is associated with worse visual memory performance in healthy young adults. J Alzheimers Dis. 2017;59(2):675-681. doi: 10.3233/JAD-170118. PMID: 28671115; PMCID: PMC5523837. (**IF: 3,476**)
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V.3. Presentations related to this thesis

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3. Juhász C, **John F**, Naveh A, Barger GR, Bomzon Z, Mittal S. Electric field intensities delivered by tumor-treating fields (TTFields) to glioblastoma regions: effect on treatment response assessed by amino acid PET. Neuro Oncol 2018;20 (suppl 6): vi187. Presented at the Annual Meeting of the Society for Neuro-Oncology, New Orleans, LA, November 15-18, 2018. https://doi.org/10.1093/neuonc/noy148.775
4. Jeong JW, Lee MH, **John F**, Robinette NL, Amit-Yousif A, Barger GR, Shah KD, Mittal S, Juhász C. Automatic detection of high amino acid uptake regions in glioblastoma from multi-modal MRI: A full 3D U-net study of deep learned PET data. Neuro Oncol 2018;20 (suppl 6): vi189. Presented at the Annual Meeting of the Society for Neuro-Oncology, New Orleans, LA, November 15-18, 2018. https://doi.org/10.1093/neuonc/noy148.785
5. Muzik O, **John F**, Mittal S, Juhász C. Fluorine-18-labeled PET radiotracers for imaging tryptophan uptake and metabolism in brain tumors. Neuro Oncol, 2019;21 (Supplement_3). Presented at the Meeting of the European Association of Neuro-Oncology, Lyon, September 19-22, 2019. https://doi.org/10.1093/neuonc/noz126
6. **John F**, Barger GR, Mittal S, Juhász C. Depression in patients with primary brain tumors: Relation to clinical variables and tumor characteristics. Neuro Oncol, 2019;21 (Supplement_3). Presented at the Meeting of the European Association of Neuro-Oncology, Lyon, September 19-22, 2019. https://doi.org/10.1093/neuonc/noz126
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