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Integrated imaging of [^{11}C]-PBR28 PET, MR diffusion and magnetic resonance spectroscopy ^{1}H-MRS in amyotrophic lateral sclerosis

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ABSTRACT

Objective: To determine the relationship between brain tissue metabolites measured by *in vivo* magnetic resonance spectroscopy (^{1}H-MRS), and glial activation assessed with [^{11}C]-PBR28 uptake in people with amyotrophic lateral sclerosis (ALS).

Methods: Forty ALS participants were evaluated clinically using the revised ALS functional rating scale (ALSFRS-R) and upper motor neuron burden (UMNB). All participants underwent simultaneous brain [^{11}C]-PBR28 PET and MR imaging including diffusion tensor imaging to acquire fractional anisotropy (FA). [^{11}C]-PBR28 uptake was measured as standardized uptake values normalized by whole brain mean (SUVR). ^{1}H-MRS metabolite ratios (myo-inositol/creatine, mI/Cr; *N*-acetylaspartate/creatine, NAA/Cr) were measured within the precentral gyri and brain stem (regions known to be involved in ALS pathophysiology), and precuneus (which served as a control region). Whole brain voxel-wise correlation analyses were employed to identify brain regions exhibiting an association between metabolites within the VOIs and [^{11}C]-PBR28 uptake.

Results: In the precentral gyri, [^{11}C]-PBR28 uptake correlated positively with mI/Cr and negatively with NAA/Cr. The same correlations were not statistically significant in the brain stem, or in the control precuneus region. Whole brain voxel-wise correlation analyses between the estimated brain metabolites within the VOIs and SUVR were highly correlated in the precentral gyri. Decreased FA values in the precentral gyri were correlated with reduced NAA/Cr and elevated mI/Cr. Higher UMNB was correlated with increased [^{11}C]-PBR28 uptake and mI/Cr, and decreased NAA/Cr. ALSFRS-R total score correlated positively with NAA/Cr and negatively with mI/Cr.

Conclusion: Integrated PET-MR and ^{1}H-MRS imaging demonstrates associations between markers for neuronal integrity and neuroinflammation and may provide valuable insights into disease mechanisms in ALS.

1. Introduction

Genetic and postmortem human brain pathology studies implicate glial activation and neuroinflammation in ALS (Alexianu et al., 2001; Butovsky et al., 2012; Boillee et al., 2006; Cady et al., 2014; Brettschneider et al., 2012). In contrast to postmortem pathological studies, molecular neuroimaging provides an opportunity to study and track ALS mechanisms, *in vivo,* and to potentially measure the biological

Abbreviations: ^{1}H-MRS, proton magnetic resonance spectroscopy; ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS functional rating scale; Cr, creatine; DTI, diffusion tensor imaging; FA, fractional anisotropy; mI, myo-inositol; MEMPRAGE, multi-echo magnetization prepared rapid acquisition gradient echo; NAA, *N*-acetylaspartate; PRESS, point-resolved spectroscopy; PBR, peripheral benzodiazepine receptor.; SUV, standardized uptake value; SUVR, standardized uptake value normalized to whole brain mean; TSPO, translocator protein; UMNB, upper motor neuron burden; VOI, volume of interest

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effects of experimental treatments (Jucaite et al., 2015).

Upon activation, microglia and astrocytes undergo increased expression of the 18 kDa translocator protein (TSPO), previously known as the peripheral benzodiazepine receptor (PBR) (Rupprecht et al., 2010). [^{11}C]-PBR28 is a second-generation positron emission tomography (PET) radiotracer for TSPO (Lavisse et al., 2012; Brown et al., 2007; Briard et al., 2008), and as such is used to image neuroinflammation *in vivo* (Albrecht et al., 2016). [^{11}C]-PBR28 was developed to overcome challenges associated with the first-generation TSPO radioligands. [^{11}C]-PBR28 was shown to exhibit 80 times more specific binding compared to the first generation radioligand [^{11}C] -(*R*)-PK11195 in non-human primates (Sridharan et al., 2017; Kreisl et al., 2010).

Glial activation measured by [^{11}C]-PBR28 PET is increased in the precentral gyri in patients with ALS and other motor neuron diseases (Paganoni et al., 2018; Zurcher et al., 2015), and this increase co-localizes with microstructural alterations measured by changes in fractional anisotropy (FA) and cortical thickness (Alshikho et al., 2016). Here, we employ a multimodal neuroimaging approach using [^{11}C]-PBR28 PET, magnetic resonance spectroscopy (^{1}H-MRS), and diffusion tensor imaging (DTI) to evaluate the relationship between glial activation and brain structural integrity, as well as the clinical outcome measures in ALS patients.

N-acetylaspartate (NAA) and myo-inositol (mI) are brain metabolites that can be measured by ^{1}H-MRS and are thought to serve as markers of neuronal/axonal integrity and neuroinflammation/gliosis, respectively (Moffett et al., 2007; Brand et al., 1997).

The relationship between molecular measurements derived from PET modalities and ^{1}H-MRS brain tissue metabolites has never been tested in patients with ALS. This molecular multimodal imaging approach may provide invaluable insights into disease mechanisms and could guide future therapeutic interventions.

2. Materials and methods

2.1. Standard protocol approvals, registrations, and patient consents

This study was approved by the Partners institutional review board (IRB) and the radioactive drug research committee (RDRC) at Massachusetts General Hospital (MGH), Boston, MA. All participants provided written informed consent for study participation according to the declaration of Helsinki.

2.2. Study participants and clinical assessments

Between March 2014 and December 2016, sixty-three individuals were genotyped for TSPO Ala147Thr polymorphism, which predicts [^{11}C]-PBR28 binding affinity (Guo et al., 2014; Owen et al., 2012), and five low binders (7.8%) were excluded during the screening phase of the study. Forty ALS participants, high or mixed TSPO binders, who successfully completed PET-MR brain imaging and fulfilling the revised El Escorial diagnostic criteria for possible, probable, lab-supported probable, or definite ALS, were included in the study (Brooks et al., 2000). The clinical assessment of ALS participants included the revised ALS functional rating scale (ALSFRS-R) (Cedarbaum et al., 1999), and the upper motor neuron burden scale (UMNB) (Zurcher et al., 2015). Participants were excluded if they had any contraindication to undergo MR imaging ($n = 3$), or any current use of steroids, immunosuppressants ($n = 2$), benzodiazepines or non-steroidal anti-inflammatory medications. Patients with frontotemporal dementia, chronic inflammatory conditions, or recent history of an active infection were also excluded.

2.3. PET-MR data acquisition

[^{11}C]-PBR28 was produced in-house as previously described (Imaizumi et al., 2007). At injection time, the mean [SD] bolus injection of [^{11}C]-PBR28 was 465.31 [77.29] MBq. All imaging studies were performed at a single site using a Siemens 3 T Magnetom Tim Trio scanner (Siemens Erlangen, Germany) equipped with an 8-channel head coil, and a head-only PET camera to simultaneously acquire PET-MR images. The PET scanner consisted of dedicated brain avalanche photodiode based PET scanner that operated in the bore of a 3 T whole-body MR scanner. The spatial resolution in the center field-of-view was < 3 mm. Additional information about the PET system was described in detail in previous publications (Catana et al., 2010; Kolb et al., 2012).

MR data acquisition included:

1) T1-weighted 3D multi-echo magnetization prepared rapid acquisition gradient echo (MEMPRAGE) for the purposes of anatomical localization, spatial normalization as well as attenuation correction for the PET data (Izquierdo-Garcia et al., 2014).
2) Diffusion tensor imaging (DTI) data were acquired using a single-shot, spin-echo and echo-planar imaging (EPI) sequence ($b = 3000$ s/mm^2) with twice refocused spin echo diffusion preparation (Q-ball imaging). Each set of raw diffusion data included sixty diffusion directions and eight low-b images.
3) Four ^{1}H-MRS volumes of interest (VOIs) of 8 cm^3 were placed based on the MEMPRAGE images in the left and right precentral gyri including the underlying white matter, in the brain stem as regions of interest, and in the precuneus as a control region, as the latter is not known to be implicated in ALS pathophysiology. We placed one voxel in the precuneus as a bilateral structure because it is a medial structure, and the left and right precuneus are close to each other. Since the precuneus is not known to be involved in ALS, we didn't need to make a distinction between the left and right precuneus, and we used it as one control region. These placements of the VOIs were done manually by an experienced neurologist as well as a spectroscopist. Prior to data acquisition, the ^{1}H-MRS VOIs underwent an automatic shim routine based on gradient double acquisition (GRE-shim) using first and second order shims followed by first order manual shimming. A point-resolved spectroscopy (PRESS) sequence was used to measure brain metabolites. The acquisition parameters for the MR data are summarized in Supplementary Table 1.

2.4. Data processing

The PET images were acquired 60–90 min post radiotracer injection, and [^{11}C]-PBR28 uptake was quantified as standardized uptake value ratio (SUVR) normalized by whole brain mean (Zurcher et al., 2015; Alshikho et al., 2016). Further details are summarized in prior publication (Izquierdo-Garcia et al., 2014). The preprocessing steps of the raw diffusion data were performed using FMRIB Software Library FSL (v5.0.9, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Diffusion data were examined carefully for motion artifacts, and corrected for eddy current-induced distortions and head motion (Andersson and Sotiropoulos, 2016).

After ^{1}H MRS acquisition, data were exported as binary remote data access (RDA) files which include information about the geometrical characteristics of the VOIs (*i.e.* location, dimensionality, and its rotation in space) in the native space of participants. This procedure allowed the creation of 3D masks representing the exact location and orientation of the ^{1}H-MRS voxel placement using the “mri_volsynth” tool in Freesurfer (v6·0, https://surfer.nmr.mgh.harvard.edu/), which were then used to quantify all the other PET-MR measurements within the VOIs. Tools in Freesurfer were used to compute PET-MR measures within the VOIs.

LCModel (v6.3) was used to quantify myo-inositol (mI), creatine (Cr), and *N*-acetylaspartate (NAA), within the VOIs. The analysis was performed within the chemical shift range (0.5–4 ppm). The concentrations of mI and NAA were normalized by Cr concentration and expressed as ratios of mI/Cr and NAA/Cr as commonly done (Pohl

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