NeuroImage: Clinical 19 (2018) 213–221

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

# Hippocampal metabolites in asthma and their implications for cognitive function

Juliet L. Kroll[a,*], Ashton M. Steele[a], Amy E. Pinkham[b], Changho Choi[c], David A. Khan[d], Sheenal V. Patel[d], Justin R. Chen[d], Sina Aslan[b,e,f], E. Sherwood Brown[f], Thomas Ritz[a,*]

[a] Department of Psychology, Southern Methodist University, Dallas, TX, USA
[b] School of Behavioral and Brain Sciences, The University of Texas, Dallas, TX, USA
[c] Department of Radiology, The University of Texas Southwestern Medical Center, Dallas, TX, USA
[d] Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX, USA
[e] Advance MRI LLC, Frisco, TX, USA
[f] Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, TX, USA

ARTICLE INFO

*Keywords:*
Hippocampus
$^{1}$H-MRS
Structural magnetic resonance imaging
Asthma
Cognition
*N*-acetylaspartate
Glutamate
Creatine

ABSTRACT

Emerging research indicates that individuals with asthma have an increased risk of cognitive impairment, yet the associations of asthma with neural correlates of memory remain relatively unknown. The hippocampus is the predominant neural structure involved in memory, and alterations in the hippocampal metabolic profile are observed in individuals with mild cognitive impairment. We therefore hypothesized that individuals with asthma may have altered hippocampal metabolites compared to healthy controls.

Structural magnetic resonance imaging (sMRI) and proton magnetic resonance spectroscopy ($^{1}$H-MRS) were used to compare hippocampal volume and metabolites of otherwise healthy adults with and without asthma (N = 40), and to study the association of these measures with cognitive function and asthma-related variables. Participants underwent 3-Tesla sMRI and $^{1}$H-MRS, with the volume of interest placed in the left hippocampus to measure levels of *N*-acetylaspartate (NAA), glutamate (Glu), creatine (Cr), and myo-inositol (MI), as indicators of neuronal viability, cellular activity, cellular energy reserve, as well as glial activation.

Individuals with asthma had lower hippocampal NAA compared to healthy controls. For all participants, poorer cognitive function was associated with reduced NAA and Glu. For individuals with asthma, poorer cognitive function was associated with reduced disease control. Additionally, short-acting rescue bronchodilator use was associated with significantly lower NAA, and Glu, whereas inhaled corticosteroid use was related to significantly higher Cr and in tendency higher NAA and Glu. All findings controlled for left hippocampal volume, which was not different between groups.

These findings highlight that asthma and/or its treatment may affect hippocampal chemistry. It is possible that the observed reductions in hippocampal metabolites in younger individuals with asthma may precede cognitive and hippocampal structural deficits observed in older individuals with asthma.

## 1. Introduction

Emerging research indicates that individuals with asthma across the life span suffer from higher rates of cognitive and memory impairment compared to the healthy population (Irani et al., 2017); however, biological correlates of these behavioral deficits remain unknown. A recent meta-analysis synthesizing over 4148 participants, found a medium effect sized relation between asthma and reduced cognitive function (Irani et al., 2017), and in a large community sample of individuals over 55 years, individuals with asthma had a 78% increased risk for the presence of mild cognitive impairment (Caldera-Alvarado et al., 2013). Despite an accumulation of studies indicating the risk of cognitive deficits in asthma, the impact of asthma on neural regions involved in memory and their chemistry remains relatively unexplored. Central nervous system (CNS) processes in asthma and dyspnea have recently attracted attention (Binks et al., 2014; Von Leupoldt et al., 2009a; Peiffer et al., 2008; Evans, 2010; Rosenkranz et al., 2012; Pattinson, 2015; Raux et al., 2013); however, any influence of asthma on neural regions involved in memory, has only been explored in one study, observing smaller hippocampal volumes in middle aged individuals with

* Corresponding authors at: Department of Psychology, Southern Methodist University, 6116 N. Central Expressway, Suite 1160, Dallas, TX 75206, USA.
*E-mail addresses:* jkroll@smu.edu (J.L. Kroll), tritz@smu.edu (T. Ritz).

https://doi.org/10.1016/j.nicl.2018.04.012
Received 20 November 2017; Received in revised form 7 March 2018; Accepted 11 April 2018
Available online 12 April 2018

asthma (Carlson et al., 2017). The influence of asthma on neural chemistry has, to the best of our knowledge, not been explored.

The primary neural region involved in memory is the hippocampus, a structure integral for encoding episodic memory and memory consolidation (Dudek et al., 2016). Changes in hippocampal volume and chemistry often coincide with reduced cognitive performance (Brown et al., 2004; Kantarci et al., 2002); however, no studies have examined the hippocampal chemistry of patients with asthma.

Neuroimaging technology has advanced from purely structural insights and functional imaging to non-invasive identification of chemical metabolite markers of CNS activity through magnetic resonance spectroscopy ($^1$H-MRS), a technology offering valuable in-vivo neural information, which was once otherwise limited to animal models of memory (Maddock and Buonocore, 2012). MRS can capture the metabolite *N*-acetylaspartate (NAA), an indicator of neuronal density and integrity; myo-inositol (MI), a putative marker of glial activation; glutamate (Glu), an excitatory neurotransmitter; and creatine (Cr), which additionally includes phosphocreatine and is used as a marker for cellular energy and metabolism (Allaili et al., 2015). NAA is the second most concentrated molecule in the brain after Glu and provides a critical source of acetate for myelin lipid synthesis in oligodendrocytes. NAA facilitates energy metabolism in neuronal mitochondria, and is therefore used as a putative marker of neuronal number, health, and viability (Maddock and Buonocore, 2012). MI is preferentially concentrated in glial cells and is used as a putative marker of microglial activation. Neuroinflammation is characterized by an increase in MI, and an increase of MI in neural regions has been found to be associated with and precede dementia (Voevodskaya et al., 2016; Targosz-Gajniak et al., 2013). Glu is the most prevalent excitatory neurotransmitter and its role is critical for the establishment of long term potentiation (LTP), which strengthens neural connections leading to gains in working and declarative memory (Rupsing et al., 2011). Cr is a precursor of adenosine triphosphate and therefore an indicator of cellular energy metabolism and storage, thought to be a relatively stable neural metabolite in both health and disease (Maddock and Buonocore, 2012; Allaili et al., 2015). Abnormalities in these four neural metabolites (deficits, elevations, or changes in their ratios) are observed in those with cognitive impairment, and have even been found to predict disease progression and future cognitive decline (Tumati et al., 2013; Modrego et al., 2011; Voevodskaya et al., 2016; Targosz-Gajniak et al., 2013; Rupsing et al., 2011).

Hippocampal gray matter volume deficits and alterations in hippocampal metabolites are additionally observed in chronic pulmonary inflammatory disease states, including COPD (Shim et al., 2001; Li and Fei, 2013; Esser et al., 2016); however, to the best of our knowledge, there are no studies examining hippocampal metabolites in asthma. Patients with asthma may be uniquely influenced by natural sequelae of a chronic systemic inflammatory disease, moments of hypoxia, asthma medication, and/or behavioral influences commonly associated with asthma including diminished sleep quality. Outside of the context of asthma, these factors independently demonstrate detectable influences on the hippocampus and cognition in both human and animal studies (Guo et al., 2013; Takada et al., 2015; Brown, 2009; Elcombe et al., 2017). We therefore hypothesized that hippocampal metabolites would be altered in asthma compared to healthy controls, and further hypothesized that lower levels of NAA and Glu would be associated with poorer cognitive function. We additionally hypothesized that asthma medication would demonstrate influences on hippocampal metabolites. As prior research suggests that hippocampal volume can be reduced in asthma (Carlson et al., 2017), we also analysed hippocampal structure to exclude the possibility that differences in metabolite levels were secondary to hippocampal volume. Studies in patients receiving chronic corticosteroid treatment have found no significant differences between left and right hippocampal metabolites (Brown et al., 2004), consistent with reviews of hippocampal metabolites in mild cognitive impairment (Maddock and Buonocore, 2012). Individuals with greater cognitive deterioration have shown lower levels of NAA in the left temporal lobe (Maddock and Buonocore, 2012), and we therefore focused our analyses on the left hippocampus.

## 2. Methods and materials

Additional methodological details are provided in the online supplement.

### 2.1. Participants

Twenty patients with a physician's diagnosis of asthma were compared to twenty age- and gender-matched healthy controls. Exclusion criteria for all participants included: neurological or cardiovascular disease, any other chronic inflammatory disease, lung disease besides asthma, history of smoking, current major depressive episode, current or recent history (within one year) of substance related disorders including alcohol abuse, recreational drug use, history of any manic episode, and symptoms of schizophrenia, bipolar disorder, or psychosis. Individuals who used corticosteroids (oral and injected) within the past 3 months were additionally excluded. As a precaution for the scanning environment, participants with values of forced expiratory volume in one-second ($FEV_1$) % predicted < 70%, were excluded (National Heart, Lung, and Blood Institute (NHLBI), 2007). $FEV_1$ is a clinical standard measure of mechanical lung function captured by spirometry.

### 2.2. General procedure

Participants completed questionnaires followed by a trained experimenter presentation of the Montreal Cognitive Assessment (MoCA) and spirometry. Within one week, administration of the Asthma Control Questionnaire (ACQ) and spirometry were repeated immediately prior to magnetic resonance imaging. Individuals with asthma were asked to refrain from taking rescue inhalers the day of either session and were encouraged to reschedule if needed. This study was approved by the University of Texas Southwestern Medical Center (STU 082011-038) and Southern Methodist University (2015-007-RITT) Institutional Review Boards. Written informed consent was obtained from all participants.

### 2.3. Magnetic resonance spectroscopy acquisition and analysis

MR assessments were carried out on a whole-body 3 T scanner (Philips Medical Systems, Best, The Netherlands), equipped with a whole-body coil for RF transmission and an 32-channel phased-array head coil for reception. Water-suppressed point-resolved spectroscopy (PRESS) data were acquired with TR = 2 s, TE = 112 ms, sweep width = 2.5 kHz, number of sampling points = 2048, and number of signal averages (NSA) = 256. Water suppression was obtained with a vendor-supplied four-pulse variable-flip-angle sub-sequence. First and second order shimming was carried out, using the fast automatic shimming technique by mapping along projections (FASTMAP). The RF carrier frequencies of the PRESS sequence were set at 2.5 ppm and were adjusted for $B_0$ drifts in each excitation using a vendor-supplied tool (Frequency Stabilization). Unsuppressed water was acquired from the voxel for eddy current compensation and multi-channel combination. Spectral fitting was performed with LCModel software (Provencher, 1993), using in-house basis spectra that were computer simulated incorporating the PRESS volume localizing radio-frequency and gradient pulses. The basis set included NAA, Cr (creatine + phosphocreatine), Glu, glutamine, GABA, glycine, MI, lactate, glutathione, alanine, acetate, aspartate, ethanolamine, phosphorylethanolamine, scyllo-inositol, taurine, *N*-acetylaspartylglutamate, glucose, Cho (glycerophosphorylcholine + phosphorylcholine). The spectral fitting was conducted between 0.5 and 4.1 ppm. Cramér-Rao lower bounds (CRLB) were returned as percentage standard deviation by LCModel.