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REGION-SPECIFIC AGING OF THE HUMAN BRAIN AS EVIDENCED BY NEUROCHEMICAL PROFILES MEASURED NONINVASIVELY IN THE POSTERIOR CINGULATE CORTEX AND THE OCCIPITAL LOBE USING ^{1}H MAGNETIC RESONANCE SPECTROSCOPY AT 7 T

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Abstract—The concentrations of fourteen neurochemicals associated with metabolism, neurotransmission, antioxidant capacity, and cellular structure were measured noninvasively from two distinct brain regions using ^{1}H magnetic resonance spectroscopy. Seventeen young adults (age 19–22 years) and sixteen cognitively normal older adults (age 70–88 years) were scanned. To increase sensitivity and specificity, ^{1}H magnetic resonance spectra were obtained at the ultra-high field of 7 T and at ultra-short echo time. The concentrations of neurochemicals were determined using water as an internal reference and accounting for gray matter, white matter, and cerebrospinal fluid content of the volume of interest. In the posterior cingulate cortex (PCC), the concentrations of neurochemicals associated with energy (i.e., creatine plus phosphocreatine), membrane turnover (i.e., choline containing compounds), and gliosis (i.e., *myo*-inositol) were higher in the older adults while the concentrations of *N*-acetylaspartylglutamate (NAAG) and phosphorylethanolamine (PE) were lower. In the occipital cortex (OCC), the concentration of *N*-acetylaspartate (NAA), a marker of neuronal viability, concentrations of the neurotransmitters Glu and NAAG, antioxidant ascorbate (Asc), and PE were lower in the older adults while the concentration of choline containing compounds was higher. Altogether, these findings shed light on how the human brain ages differently depending on region.

Key words: magnetic resonance spectroscopy, human brain, aging, neurochemicals, noninvasive, cellular.

INTRODUCTION

Proton magnetic resonance spectroscopy (^{1}H MRS) can be used to noninvasively investigate age-associated neurochemical concentrations *in vivo* in the human brain. Each observable neurochemical can provide distinctive information because neurochemical levels are sensitive to different *in vivo* processes. In particular, *N*-acetylaspartate (NAA) is a putative marker of neuronal viability (Brand et al., 1993; Urenjak et al., 1993; Mountford et al., 2010; Duarte et al., 2012; Rae, 2014), creatine (Cr) and phosphocreatine (PCr) are neuronal energy substrates, glycerophosphorylcholine (GPC), phosphorylcholine (PCho), phosphorylethanolamine (PE), and *myo*-inositol (mIns) are associated with membrane turnover (Michaelis et al., 1993; Boulanger et al., 2000; Duarte et al., 2012; Rae, 2014), PE is also associated with myelination (Rao et al., 2013), *N*-acetylaspartylglutamate (NAAG) is a neuromodulatory peptide (Moffett et al., 2007; Duarte et al., 2012), ascorbate (Asc) is an antioxidant (Rice and Russo-Menna, 1998), and glutamate (Glu) is a neurotransmitter. Also, some neurochemicals are preferentially concentrated in certain cell types. For example, NAA, NAAG, Asc, and

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Abbreviations: ^{1}H MRS, proton magnetic resonance spectroscopy; AD, Alzheimer's disease; AFNI, analysis of functional neuro images; Asc, ascorbate; Asp, aspartate; CBF, cerebral blood flow; Cr, creatine; CRLB, Cramér-Rao lower bounds; CSF, cerebrospinal fluid; DMN, default mode network; FAST(EST)MAP, fast automatic mapping along projections with echo planar imaging readout; FSL, a comprehensive library of analysis tools for fMRI, MRI and DTI brain imaging data GABA,γ-aminobutyric acid; Glc, glucose; Gln, glutamine; Glu, glutamate; GM, gray matter; GPC, glycerophosphorylcholine; GSH, glutathione; Lac, lactate; mIns, *myo*-inositol; MPRAGE, magnetization-prepared rapid gradient-echo; NAA, *N*-acetylaspartate; NAAG, *N*-acetylaspartylglutamate; OCC, occipital cortex; PCC, posterior cingulate cortex; PCho, phosphorylcholine; PCr, phosphocreatine; PD, proton density; PE, phosphorylethanolamine; RF, radiofrequency; sIns, *scyllo*-inositol; SPM, statistical parametric mapping; STEAM, stimulated echo acquisition mode; Tau, taurine; tCho, choline containing compounds, glycerophosphorylcholine + phosphorylcholine; tCr, total creatine, creatine + phosphocreatine; VAPOR, variable power and optimized relaxation delay; VOI, volume-of-interest; WM, white matter.

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Glu are primarily neuronal (Rice and Russo-Menna, 1998; Moffett et al., 2007; Duarte et al., 2012; Rae, 2014). mIns is predominantly concentrated in glia (Brand et al., 1993; Duarte et al., 2012; Rae, 2014), and may be a glial marker (Brand et al., 1993; Moffett et al., 2007; Duarte et al., 2012; Rae, 2014).

Approaches other than MRS have shown that blood flow, metabolism, and connectivity in the human brain are impacted by aging and disease in a region-specific fashion. In the posterior cingulate cortex (PCC), age-associated differences in cerebral blood flow (CBF) (Martin et al., 1991) and glucose uptake (Zuendorf et al., 2003) have been documented. The PCC is the hub of the default mode network (DMN) (Leech and Sharp, 2014). The DMN is known to deteriorate during both aging (Sambataro et al., 2010; Sala-Llonch et al., 2015; Joo et al., 2016) and Alzheimer's disease (AD) (Lustig et al., 2003; Dennis and Thompson, 2014). Metabolism and blood flow in the PCC are also impacted by AD (Boulanger et al., 2000; Kantarci et al., 2007; Hof and Mobbs, 2009; Leech and Sharp, 2014; Iizuka and Kameyama, 2016), possibly because of the many types of connections that the PCC has to the hippocampus. Thus, the PCC is relevant to the neurobiology of healthy and aberrant aging. Advancing knowledge about this region and developing technology for future studies are valuable to ongoing investigation of cognitive decline.

In contrast, aging does not tend to affect the human occipital cortex (OCC). The OCC is consistently noted among regions with the least age-associated glucose uptake difference (Zuendorf et al., 2003; Kalpouzos et al., 2009). The OCC is not part of the DMN. Changes in CBF are rarely reported in this region. However, the OCC tends to be included in multi-region investigations of brain aging (Christiansen et al., 1993; Saunders et al., 1999; Eylers et al., 2016). Additionally, scanning both the PCC and the OCC improved specificity for detecting AD with ^{1}H MRS (Kantarci, 2007). Age-associated differences in neurochemical concentrations have been shown to be specific to brain region (Kaiser et al., 2005). Thus the OCC is a suitable control region to the PCC for studying aging and working toward mitigating cognitive decline.

In the PCC, NAA, total Cr (tCr = Cr + PCr), and choline containing compounds (tCho = GPC + PCho) have been measured in the context of aging using ^{1}H MRS in several studies (Robertson et al., 2001; Chang et al., 2009; Reyngoudt et al., 2012; Chiu et al., 2014; Fayed et al., 2014). Three studies reported higher tCho concentration in older adults (Robertson et al., 2001; Chiu et al., 2014; Fayed et al., 2014), while two did not find a significant difference (Chang et al., 2009; Reyngoudt et al., 2012). For tCr, two studies reported higher concentration in older adults (Reyngoudt et al., 2012; Chiu et al., 2014), while two did not find a difference (Robertson et al., 2001; Chang et al., 2009). For NAA, conflicting results have been reported. One study reported higher (Chiu et al., 2014) and one study lower (Fayed et al., 2014) age-associated NAA, and three other studies (Robertson et al., 2001; Chang et al., 2009; Reyngoudt et al., 2012) did not find a significant difference. Higher mIns (Reyngoudt et al., 2012; Fayed et al., 2014) and lower Glu (Chang et al., 2009; Fayed et al., 2014) have also been reported in the PCC in older adults. In summary, age-associated differences in NAA concentration in the PCC are controversial, and only a few studies have reported differences in tCr, tCho, mIns, and Glu.

NAA, tCr, and tCho concentrations have also been measured on several occasions in the OCC in the context of aging (Christiansen et al., 1993; Saunders et al., 1999; Eylers et al., 2016). For tCho and tCr, the absence of significant age-associated difference has been consistently observed (Christiansen et al., 1993; Saunders et al., 1999; Eylers et al., 2016). The absence of significant difference has also been reported for mIns (Saunders et al., 1999) and for NAA on one occasion (Saunders et al., 1999). Lower NAA in older adults has been reported on a few occasions (Christiansen et al., 1993; Eylers et al., 2016), although under circumstances that could have been impacted by age-associated differences in the transverse relaxation time constant (T_2) of NAA. The T_2s of NAA, tCr and tCho have been shown to be shorter in older adults (Marjanska et al., 2013). Therefore, further investigation is warranted of whether there are age-associated differences in neurochemical concentrations in this region that appears to be minimally impacted by aging.

The goal of this project was to quantify brain region-specific neurochemical concentrations in the context of human aging with greater sensitivity and accuracy than has been achieved in the past. Sensitivity and specificity gains that can be achieved using ultra-high field, 7 T, ^{1}H MRS were expected to: increase power for measuring age-associated differences, add perspective to the small number of studies that have reported such differences, and detect differences in additional neurochemicals. Scanning was implemented at ultra-short echo time to resolve the ambiguity that arises from age-associated differences in T_2 of neurochemicals.

EXPERIMENTAL PROCEDURES

Subjects

Seventeen young adults (seven males, ten females; age: 21 ± 1 (mean ± standard deviation) years; age range 19–22 years) and sixteen older adults (nine males, seven females; age: 78 ± 5 years; age range 70–88 years) provided informed consent according to procedures approved by the Human Subjects' Protection Committee at the University of Minnesota, Institutional Review Board. All participants underwent an MRI exam at 7 T, and five young and six older participants underwent two additional retest scans (for a total of three scans at approximately weekly intervals). Dietary influence was controlled by recruiting participants who consumed fewer than five fruits and vegetables per day and no more than the recommended daily allowance of supplements. Circadian variance (O'Neill et al., 1983) was controlled by scanning all participants between 9 AM and 12 PM. Exclusion criteria for all participants were claustrophobia, non-removable metallic