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# Frontal Gamma-Aminobutyric Acid Concentrations Are Associated With Cognitive Performance in Older Adults

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## ABSTRACT

**BACKGROUND:** Gamma-aminobutyric acid (GABA), the brain's principal inhibitory neurotransmitter, has been associated with perceptual and attentional functioning. Recent application of magnetic resonance spectroscopy (MRS) provides in vivo evidence for decreasing GABA concentrations during adulthood. It is unclear, however, how age-related decrements in cerebral GABA concentrations contribute to cognitive decline, or whether previously reported declines in cerebral GABA concentrations persist during healthy aging. We hypothesized that participants with higher GABA concentrations in the frontal cortex would exhibit superior cognitive function and that previously reported age-related decreases in cortical GABA concentrations continue into old age.

**METHODS:** We measured GABA concentrations in frontal and posterior midline cerebral regions using a Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) $^{1}$H-MRS approach in 94 older adults without history or clinical evidence of mild cognitive impairment or dementia (mean age, 73 years). We administered the Montreal Cognitive Assessment to assess cognitive functioning.

**RESULTS:** Greater frontal GABA concentrations were associated with superior cognitive performance. This relation remained significant after controlling for age, years of education, and brain atrophy. GABA concentrations in both frontal and posterior regions decreased as a function of age.

**CONCLUSIONS:** These novel findings from a large, healthy, older population indicate that cognitive function is sensitive to cerebral GABA concentrations in the frontal cortex, and GABA concentration in frontal and posterior regions continue to decline in later age. These effects suggest that proton MRS may provide a clinically useful method for the assessment of normal and abnormal age-related cognitive changes and the associated physiological contributors.

*Keywords:* Aging, Cognition, GABA, γ-Aminobutyric, MEGA-PRESS, MRS

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Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the human nervous system and plays a fundamental role in central nervous system function (1). GABA neurotransmission is involved in nearly all neuronal coding and processing throughout the brain. It directly influences membrane potentials through ionic $GABA_A$ receptors and modulates both short- and longer-term neuronal activity via G-protein coupled $GABA_B$ receptors, modifying synaptic and network plasticity (2–6). Given this connection to synaptic plasticity, GABA has been studied in the context of the aging brain. Recent work demonstrates that GABA concentrations decline with age (7), and rodent models have shown age-related decreases in a GABA synthetic enzyme, glutamic acid decarboxylase (8). However, the relation between these long-term decreases in GABA concentrations and age-related declines in cognitive function has yet to be determined.

A large body of GABA studies relies on examination of downstream pharmacological effects of GABAergic agents (e.g., benzodiazepines) and animal models. This work links GABA to age-related cognitive decline in rodents (9), specifically noting the importance of GABA as a modulator of memory encoding (10,11). Although such studies provide a strong foundation for investigations into the relation between GABA and cognition, these methods make extensions of their results to more broad discussions of human cognition challenging. Relevant to the question at hand, then, is the development of Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) (12,13) for GABA-edited magnetic resonance spectroscopy (MRS) (12,14,15). This acquisition sequence allows for relatively rapid and reliable quantification of GABA concentrations in the brain of awake humans. Because these GABA concentrations are experimentally mutable (16,17), MEGA-PRESS more directly enables research into the regionally variable role of GABA in behavior and cognitive function.

This approach has proven to be a flexible and powerful tool for examining GABA, facilitating investigations of GABAergic contributions to specific behaviors and pathological disorders and differences in GABA concentrations between populations. Broadly, researchers have used this approach to demonstrate

 

that GABA concentrations correlate with other measures of brain activity, including functional magnetic resonance imaging indices (18,19), cerebral blood flow (19), and motor cortex gamma oscillations (20). Specifically applying this work to the intersection between GABA and cognition, several MRS studies have examined the role of GABA in sensory and motor functioning in healthy populations. Often, these studies delineate the differential importance of GABA in various brain regions for multiple sensorimotor or cognitive functions. For example, associations between sensorimotor GABA concentrations and tactile sensitivity have been demonstrated in sensorimotor cortices (21,22). GABA concentrations in the occipital cortex have been shown to relate to visual orientation discrimination (23), whereas frontal GABA concentrations correspond with working memory performance (24). Thus, some degree of specificity between cortical GABA concentration and cognitive ability seems likely. Less clear, however, is the relation between GABA and higher-order cognitive functioning and its decline in healthy aging.

Notably, although GABA concentrations tend to be stable over the short term (25), they do change over longer periods of time. A recent cross-sectional study of adults (20–76 years of age) indicated that GABA concentrations decrease with age after adolescence. This report specifically found an approximate 5% reduction in GABA concentrations with age per decade in the frontal cortex (7). Because the frontal cortex is important for numerous cognitive domains, notably those related to executive function (26–29), such a decline might correlate or even underlie alterations in related domains of cognitive function. The functional significance of these age-associated changes in GABA is not well established.

Given these considerations, the present study examined the relation between frontal and posterior GABA concentrations and cognitive function in the context of normal cognitive aging. We sought to extend previous work relating GABA and cognitive function in modality-specific cortices (e.g., occipital lobe) by investigating higher-order cognition with a general cognitive screening measure, the Montreal Cognitive Assessment (MoCA) (30). This tool, widely used in clinical settings, taps several cognitive domains, including attention/working memory, verbal memory, naming, and fluency. Because a number of these domains fall under the umbrella of executive functions, the MoCA is quite sensitive to frontal dysfunction in general (31). Convergently, older adults demonstrate changes in both frontal activation and frontally mediated cognitive functions. Thus, we placed our primary MRS voxel of interest in the frontal lobe. We predicted that GABA concentrations would continue to decrease in advanced age. We also predicted that the relation between concentrations of GABA in the frontal regions would predict general cognitive performance on the MoCA. We additionally placed a voxel in the posterior cortex to serve as a control. We predicted that, although GABA in this region would decline with age, there would be no association between GABA concentrations and global cognitive performance.

## METHODS AND MATERIALS

### Population

Ninety-four older volunteers (54 women, 40 men; age [mean ± SD], 73.12 ± 9.9 years; years of education, 16.25 ± 2.8 years; MoCA scores, 25.5 ± 2.5) were recruited from the local community. Subjects with a self-reported history of neurological or psychiatric disease on comprehensive medical questionnaires or magnetic resonance imaging (MRI) prescreening forms were excluded from the study. Subjects reported abstaining from alcohol on the day of MRS data collection. Of the 94 subjects, 89 had the frontal voxel collected, and 90 had the posterior voxel collected (due to time constraints in the imaging sequence, 5 participants had only a frontal voxel collected and 4 participants had only a posterior voxel collected). Ethical approval for the study was obtained via the University of Florida's Institutional Review Board, and all participants signed an informed consent form after discussion of the study with a study coordinator and review of the document.

### MoCA

The MoCA is a one-page cognitive assessment that takes approximately 10 minutes to administer. A score of 0–30, reflecting general cognitive function, is derived from performance on tasks assessing the following cognitive domains: verbal memory, visuospatial abilities, executive functions, attention, working memory, naming, verbal fluency, repetition, and orientation to time and place (30). One point was added to the scores of participants who had 12 years of education or less (30). Using the MoCA total score in this analysis has a number of advantages. First, the MoCA is a widely used clinical tool with good psychometric properties (e.g., test-retest reliability and internal consistency). It has better sensitivity to mild cognitive impairment and other forms of cognitive decline, including Korsakoff's syndrome, than the Mini-Mental State Examination (32). Thus, a comparison between MoCA performance and GABA concentration allows for a discussion of these mechanisms in a translational context. Precisely because this measure is both sensitive and quick to administer, the MoCA is an efficient test to use in the clinical space. This analysis, then, allows for extension of previous GABA studies to a highly clinically relevant tool. The MoCA, however, does present a notable disadvantage. This instrument is useful when interpreted as a whole, but is not as useful at the level of subscale analysis, because the domains frequently are probed with three to five questions. This small range limits variability, and in healthy populations, many domains experience a ceiling effect. Therefore, the utility of this instrument is somewhat limited to general cognitive performance.

### MRS Acquisition and Analysis, $^{1}$H-MRS Spectroscopy, Spectrum Editing, and Volume-of-Interest Refraction

All scanning was performed on a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using a 32-channel head coil. A T1-weighted anatomical image (magnetization-prepared rapid gradient-echo; repetition time/echo time = 8 ms/3.7 ms, 1-mm$^3$ isotropic voxels) was acquired for MRS voxel placement and segmentation. GABA-edited MRS data were acquired using the MEGA-PRESS sequence (12). PRESS localization was achieved with minimum-phase amplitude-modulated excitation pulses (2-kHz bandwidth) and amplitude-modulated refocusing pulses (bandwidth, 1.3 kHz), as shown in Figure 3 of Mullins *et al.* (14). Editing was performed with 14-ms