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Age-Related Declines in Occipital GABA are Associated with Reduced Fluid Processing Ability

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Abstract

Rationale and Objectives: Healthy aging is associated with pervasive declines in cognitive, motor, and sensory functioning. There are, however, substantial individual differences in behavioral performance among older adults. Several lines of animal research link age-related reductions of gamma-aminobutyric acid (GABA), the brain's primary inhibitory neurotransmitter, to age-related cognitive, motor, and sensory decline. Our study used proton magnetic resonance spectroscopy (MRS) at 3T to explore whether occipital GABA declines with age in humans and whether individual differences in occipital GABA are linked to individual differences in fluid processing ability.

Materials and Methods: We used a MEGA-PRESS sequence that combines frequency spectral editing with a point-resolved spectroscopy sequence to quantify GABA. Spectra were obtained from a $30 \times 30 \times 25$ mm voxel placed in the occipital cortex of 20 young adults (mean age 20.7 years) and 18 older adults (mean age 76.5 years). Participants also performed 11 fluid processing tasks outside the scanner, the results of which were *z*-scored and averaged to calculate a summary measure of fluid processing ability. Regression analysis was employed to determine the relationship between GABA concentrations in the occipital cortex and a summary measure of fluid processing ability.

Results: Occipital GABA was significantly lower in older participants compared to the younger participants. We also observed a significant positive relationship between occipital GABA and fluid processing ability. In fact, higher GABA was associated with better task performance in 10 of the 11 tasks.

Conclusion: These findings suggest that GABA levels decline with age in humans and are associated with declines in fluid processing ability.

Keywords

Magnetic resonance spectroscopy; Aging; MEGA-PRESS; Gamma-aminobutyric acid; Normal brain

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INTRODUCTION

Healthy aging is associated with reduced fluid processing as indexed by impairments in working memory, long-term memory, and speed of processing. However, there are substantial individual differences in the effects of age on cognition. Some healthy older adults exhibit significant fluid processing impairments while others do not (13,15,39). Given the enormous personal and societal costs that are associated with age-related cognitive decline, it is important to determine factors that influence the severity of this phenomenon.

One factor may be age-related reductions of gamma-amino-butyric acid (GABA), the primary inhibitory neurotransmitter of the brain. Genes related to GABA-ergic function are down-regulated during normal aging in humans and rhesus macaques (20), and several lines of research in animals suggest that GABA function declines with age. For example, the number of GABA-immunoreactive neurons declines with age in the inferior colliculus (6), hippocampus (35), and striate visual cortex (17). There are also age-related reductions in baseline GABA, GABA release, and GABA receptor binding (6).

Furthermore, GABA function is linked with behavior in animals. For example, reduced hippocampal GABA(B) receptor expression is associated with spatial learning impairments in rats (22). In addition, apolipoprotein E4 knock-in mice exhibit age-related reductions in GABAergic interneurons that are associated with learning and memory impairments. However, those impairments are eliminated by daily injections of a GABA(A) receptor potentiator (1) and return if the injections are subsequently with-held (37). These findings raise the possibility that age-related declines of cognition are associated with age-related declines of GABA functioning.

Recently, it has become possible to study GABA in humans using magnetic resonance spectroscopy (MRS), a noninvasive technique that can estimate regional metabolite levels in vivo. Using this technique, researchers have revealed age-related declines in GABA in frontal, parietal, and posterior brain regions (11,12,27). MRS studies have also reported relationships between GABA measures and behavioral performance in a number of domains, including visual function (9,40), motor control (5), tactile function (14,28), and executive function (18,23,40).

These studies suggest that GABA levels tend to decline with age and that GABA function predicts behavior. Recent evidence also suggests that cognitive declines associated with aging may be related to age-related declines in GABA concentration, with declines in frontal GABA concentration associated with lower scores on the Montreal Cognitive Assessment, a widely used screening assessment for detecting cognitive impairment (27).

Here, we investigated whether age-related declines of GABA are associated with a very important aspect of age-related cognitive decline: reduced fluid processing ability (e.g., speed of processing and executive functioning). The aim of the present study was to test this hypothesis by combining MR spectroscopy with behavioral methods for assessing cognitive functioning.

We focused on the occipital cortex for three reasons. First, orientation and direction discrimination decline with age at both the neural (33) and behavioral (3) levels. Second, age-related declines in the orientation selectivity of visual cortex neurons can be reversed by the administration of GABA or a GABA agonist (19), thereby demonstrating that GABA plays a causal role in visual functioning. Third, prior findings from our group indicate that functional magnetic resonance imaging measures of heightened object selectivity in the human occipital cortex are associated with increased fluid processing ability (26).

METHODS

Participants

Twenty older participant (8 males; aged, 59–87 years; mean = 76.5 years, SD = 8.73 years) and nineteen younger participants (9 males; aged 18–23 years, mean = 20.74 years, SD = 1.37 years) were recruited for this study. All participants provided informed consent following a protocol approved by the Institutional Review Board of the University of Michigan and were screened for magnetic resonance contraindications. Individuals were eligible to participate if they were right handed and between 18 and 30 years old (young group) or over 59 (older group). Exclusion criteria included pregnancy, any history of neurological or psychiatric disorder, or any history of drug or alcohol abuse.

Participants attended a behavioral testing session, followed approximately two weeks later by an imaging session (intersession interval, 2–28 days, mean = 11.97 days, SD = 7.10 days). Participants were paid \$10 per hour for the behavioral session, and \$20 per hour for the imaging session.

Behavioral Testing

During the behavioral session, participants completed the Mini-Mental State Exam, the extended range vocabulary test, and 11 fluid processing tasks. Of the 11 tasks, seven measured perceptual processing (Contour detection, Digit-symbol coding, Pattern comparison, Cambridge Face Perception Test - Upright (CFPT upright), Cambridge Face Perception Test - Inverted (CFPT inverted), Dot speed and Dot coherence), three measured executive function (Controlled Oral Word Association test (COWAT), Trail making test A and Trail making test B) and one measured memory (Cambridge Face Memory Test (CFMT)). Of importance, performance on all of these tasks typically declines with age.

CFMT, (8): Participants are introduced to six male target faces, and asked to learn each face in three views. Participants are presented with three faces and asked to choose the learned face from two distractors. For each target face, three test items contain views identical to those studied in the introduction, five present novel views and four present novel views with noise. Performance on the CFMT has been shown to decline with age (4).

Contour Detection: Participants were presented with groups of lines and asked to determine whether some of the lines formed a circle or an ellipse. A staircase procedure was used to determine how much jitter in line orientation participants could tolerate, while still

being able to make a correct judgment. Age-related impairments in contour integration have previously been observed (30).

Digit-Symbol Coding: Participants viewed nine digit-symbol pairs followed by a list of digits, and were asked to write the symbol that corresponded to each digit as quickly as possible. The number of correct symbols participants produced within 90 seconds was measured. The task was taken from the Wechsler adult intelligence scale-third edition (38), and performance on this task shows a robust age related decline from around the age of 45 (16).

Pattern Comparison (31): Participants were asked to determine if two patterns of lines were the same or different. Participants performed this task on three sets of 32 pattern pairs with 30 seconds to complete each set. The total number of correct judgments across all three sets was measured. Notably, performance on pattern comparison tasks declines with age (32).

COWAT, (2): Participants were instructed to name as many words as they could that started with a target letter in 1 minute. The target letters were “F,” “A,” and “S.” The total number of words generated across all three letters was measured. Verbal fluency measures such as this have been observed to be sensitive to the effects of aging (36).

CFPT upright (7): Participants ranked six upright faces with respect to their similarity to a target face. Average deviation from the correct rank order was measured. Performance on the CFPT upright declines with age (4).

CFPT inverted (7): Participants ranked six inverted faces with respect to their similarity to a target face. Average deviation from the correct rank order was measured. As with the CFPT upright, performance on the CFPT inverted demonstrates a marked decline with age (4).

Dot Speed: Participants viewed two groups of moving dots and were asked to determine which group was moving faster. A staircase procedure was used to find individual thresholds. Participants completed two blocks of the task, each containing approximately 55 trials. An age-related loss of sensitivity to visual motion has been observed in older individuals (34).

Dot Coherence: Participants viewed two groups of dots and determined which group moved more coherently. A staircase procedure was used to find individual thresholds. Participants completed two blocks of the task, each of which contained approximately 55 trials. An age-related deficit in motion coherence thresholds for slow speeds has been observed (34).

Trail Making Test A: Participants were asked to draw lines connecting the numbers 1–25 in order. The numbers appeared in random positions on a sheet of paper. The amount of time it took to complete the task was measured. Significant age-related increases in completion time have been observed in this task (29).

Trail Making Test B: Participants were asked to draw connecting lines between alternating numbers and letters in ascending order (e.g., 1, A, 2, B, 3, C, etc.). The characters appeared in random positions on a sheet of paper. The amount of time it took to complete the task was measured. As with the Trail Making Test A, significant age-related increases in completion time have been observed on the Trail Making Test B (29).

MR Spectroscopy

MR spectroscopy data were acquired using a 3T Phillips Ingenia system (Best, The Netherlands) with a 32-channel head coil. For each subject, we performed a T1 weighted 3D-MPRAGE sequence with 0.9 mm³ resolution for MRS voxel placement and subsequent tissue segmentation. Magnetic resonance spectroscopy spectra were collected from a 30 × 30 × 25 mm voxel placed in the primary visual cortex (Fig 1). Single-voxel point resolved spectroscopy spectra (PRESS) were collected using the following scanning parameters: TR/TE = 2000/35 ms and “VAPOR” water suppression with 32 averages (approximately 1 minute). A MEGAPRESS sequence combining frequency spectral editing with point-resolved spectroscopy was used to distinguish GABA from other metabolites. Details of this sequence were as follows: TE = 68 milliseconds (TE1 = 15 milliseconds, TE2 = 53 milliseconds); TR = 1.8 seconds; 256 transients of 2000 data points; spectral width = 2 kHz; frequency selective editing pulses (14 milliseconds) applied at 1.9 ppm (ON) and 7.46 ppm (OFF); total scan time of approximately 10 minutes per voxel; refocusing performed using an amplitude-modulated pulse “GTST1203” (length = 7 milliseconds, bandwidth = 1.2 kHz). The signal detected at 3.02 ppm using these experimental parameters is expected to contain contributions from both macromolecules and homocarnosine, and is therefore referred to as “GABA+.”

DATA PREPROCESSING/ANALYSIS

Spectral Fitting

The PRESS spectra were analyzed using LCModel (<http://s-provencher.com/lcmodel.shtml>), which estimates the concentrations of glutamate and glutamine (Glx), *N*-acetyl aspartate (NAA), choline, and Myo-inositol (Myo). GANNET, a MATLAB toolbox (10), was used to preprocess and quantify the GABA+ signal in the MEGA-PRESS scans, using the default parameters, including frequency and phase correction of time-resolved data using spectral registration (24). The MEGA-PRESS scans are more vulnerable to field drifts and movement artifacts than typical PRESS scans because of the addition of an editing pulse and the subtraction of ON and OFF scans to obtain difference spectra, potentially leading to subtraction artifacts. Frequency correction can reduce quantification errors. All spectra were visually inspected for subtraction artifacts and noise levels. All metabolite concentrations were estimated relative to creatine as occipital creatine has been shown to be stable in the aging population (21). Metabolite concentrations were only used for statistical analysis from the LC model if the Cramer-Rao bounds were less than 20%.

Statistical Analysis

Statistical analyses were performed using the Statistical toolbox of MATLAB R2016a (MathWorks, Natick). To test the hypothesis that metabolite ratios in the visual cortex are

reduced in older individuals compared to younger ones, onetailed, two-sample *t* tests were performed. Age-related differences in performance on behavioral tasks were also investigated using one-tailed, two-sample *t* tests, since lower performance was predicted in the older participants. To investigate the link between behavioral performance and GABA concentrations, a summary measure of fluid processing was extracted from the data. Performance on each of the eleven tasks was *z*-scored, resulting in eleven *z*-scores for each participant. Each of these *z*-scores reflected a participant's performance on one of the 11 tasks relative to the performance of all other participants. The eleven *z*-scores for each participant were then averaged to obtain a single summary measure of fluid processing ability. As the 11 behavioral tasks could be classified into two groups—those in which better performance was indicated by higher scores (e.g., accuracy or number of items completed) and those in which better performance was indicated by lower scores (e.g., reaction time)—the sign was flipped (from negative to positive) for the *z* scores of the tasks in which lower scores are indicative of better performance. This ensured that positive *z*-scores would always reflect better performance.

Regression analyses were employed to determine the relationship between metabolite ratios in the occipital cortex and the summary measure of fluid processing ability. The main analyses investigated relationships between GABA and fluid processing ability, but relationships between other metabolites and fluid processing ability were also explored. Following the main analyses, correlations between GABA concentration and performance on each of the individual tasks were computed. Regressions were also performed separately for young and old participant groups, to explore age-specific relationships.

RESULTS

The demographic characteristics of the participants are summarized in Table 1. We found no significant age-related differences in the mean score of Mini-Mental State Exam. Older participants performed significantly better on the extended range vocabulary test.

GABA+ spectra were unanalyzable for young and two old participants due to poor signal to noise, and PRESS spectra were unanalyzable for one old participant. Behavioral measures were collected from 18 young participants and 19 old participants. GABA+ concentrations are presented in Figure 2, and the results for all metabolites are provided in Table 2. A two-sample *t* test revealed that, as hypothesized, occipital GABA levels were significantly lower in older participants compared to younger ones ($t_{33} = 2.22$, $p < 0.05$, one-tailed). Additionally, occipital NAA and Myo concentrations were lower in the older group than in the younger group (NAA: $t_{36} = 3.03$, $p < 0.01$; Myo: $t_{36} = 2.00$, $p < 0.05$, one-tailed). Age differences for choline and Glx were not significant.

Performance on the behavioral tasks is summarized in Table 3. Consistent with prior findings (4,16,29–31,34,36), younger participants tended to perform better than older participants on these tasks. The age difference was statistically significant ($p < 0.05$, one-tailed) for eight of the tasks (CFPT upright, dot coherence, Trail Making A, Trail Making B, CFMT, contour detection, digit symbol, pattern comparison), was marginally significant for

the CFPT inverted task ($p < 0.1$, one-tailed), and was not significant for the dot speed and letter fluency tasks (both p 's > 0.1).

As predicted, higher GABA+ levels were associated with better task performance (i.e., enhanced fluid processing) as assessed by the summary measure of behavioral performance ($t_{31} = 1.84$, $p < 0.05$, one-tailed; Fig 3, Table 4). Higher Myo, NAA, and Glx levels were also associated with better task performance as assessed by this summary measure (Myo: $t_{34} = 2.70$, $p < 0.01$, one-tailed; NAA: $t_{34} = 1.87$, $p < 0.05$, one-tailed; Glx: $t_{34} = 3.36$, $p < 0.001$, one-tailed).

NAA levels are thought to reflect neuronal integrity, and given the correlation between NAA and behavior, we wondered if the association between GABA+ and behavior was due to individual differences in NAA. After controlling for NAA, the relationship between GABA+ and behavioral performance was reduced, although it was still marginally significant (partial correlation $r = .25$, $p = 0.09$, one-tailed).

We also explored relationships between GABA+ concentration and performance on individual tasks. GABA+ levels were associated with better performance in 10 of 11 tasks (Fig 4, Table 2). This relationship was statistically significant ($p < 0.05$, one-tailed) in four of the tasks (CFPT upright, dot coherence, trail making B, and COWAT), marginally significant ($p < 0.1$, one-tailed) in one task (pattern comparison), and did not reach statistical significance ($p > 0.1$) in the other six tasks.

Relationships between metabolite ratios and performance were examined in the two age groups separately, revealing that they were driven by the older group (Table 3). The relationship between GABA+ concentration and the behavioral summary measure approached significance in the older group ($t_{16} = 1.48$, $p < 0.08$, one-tailed), but not the younger group. Additionally, the relationship between behavior and Glx was significant in the older participants, but not in the young participants (Glx_O: $t_{16} = 3.34$, $p < 0.001$, one-tailed; Glx_Y: $t_{16} = 0.27$, $p = ns$).

DISCUSSION

In the present study, we found that GABA+ concentrations in the human occipital cortex decline with age, and that lower GABA+ levels predict worse fluid processing ability in older adults. These findings are consistent with the hypothesis that age-related declines of GABA functioning contribute to age-related declines of fluid processing ability. Thus, they may help to explain why some healthy older adults exhibit significant fluid processing impairments while others do not (13,15,39).

It is worth noting that the relationship between occipital GABA+ and behavior was not restricted to purely visual tasks. In fact, some of the strongest relationships were with Letter Fluency and Trail Making B, which are typically associated with executive function rather than with vision. One possible interpretation is that age-related declines in occipital GABA+ impair aspects of visual processing that support higher cognition. Another is that age-related declines in occipital GABA+ reflect declines in GABA+ throughout the brain including

prefrontal cortex. Future studies could explore if either (or both) of these potential mechanisms can explain the relationship that we have observed.

When we investigated the relationship between GABA+ concentrations and fluid processing while controlling for individual differences in NAA levels, the relationship was weaker, although still marginally significant. This trend suggests that the relationship between GABA+ and behavior may be related to declines in neuronal integrity, but cannot be completely explained by them.

More broadly, the present findings are consistent with prior work involving nonhuman primates that has related reductions of occipital GABA to age-related declines of visual processing. For example, Leventhal et al., (19) found that the receptive fields of neurons in the visual cortex were less direction and orientation specific in old macaques, relative to young macaques. Interestingly, the administration of GABA, or a GABA agonist, to old neurons restored their specificity to youth-like levels, while the administration of a GABA antagonist to neurons in young monkeys reduced their specificity to that of neurons in older monkeys. This prior work suggests that GABA influences behavior by affecting the specificity of neural representations. Specifically, as GABA declines with age, neural representations may become less specific or distinct, thereby undermining behavioral performance.

A growing body of functional MRI findings in humans is consistent with this hypothesis. For example, Park et al. (25) found that the neural responses elicited by faces, places and words were less specialized in older adults compared to younger adults. Further, reduced neural distinctiveness is associated with reduced fluid processing ability in older adults (26). These findings, along with the present results, suggest the possibility that reductions of GABA in old age lead to declines in neural distinctiveness, which, in turn, contribute to age-related cognitive decline. Of course, the present study was purely correlational. We are therefore unable to infer a causal relationship between reduced GABA levels and fluid processing impairments. One potential way to overcome this limitation would be to manipulate GABA levels pharmacologically via the administration of drugs that affect the GABA system (e.g., benzodiazepines). We are currently pursuing such a line of research.

In conclusion, our findings indicate that human occipital GABA+ concentrations decline with age, and that individual differences in GABA are related to individual differences in fluid processing ability. These findings are consistent with the hypothesis that age-related declines in GABA may contribute to some of the age-related cognitive impairments that characterize healthy aging.

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Abbreviations

CFMT	Cambridge Face Memory Test
CFPT inverted	Cambridge Face Perception Test - inverted

CFPT upright	Cambridge Face Perception Test -upright
Cho	Choline
COWAT	Controlled Oral Word Association Test
Cr	Creatine
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
Glx	Glutamate and Glutamine
Myo	Myo-inositol
NAA	N-Acetyl Aspartate

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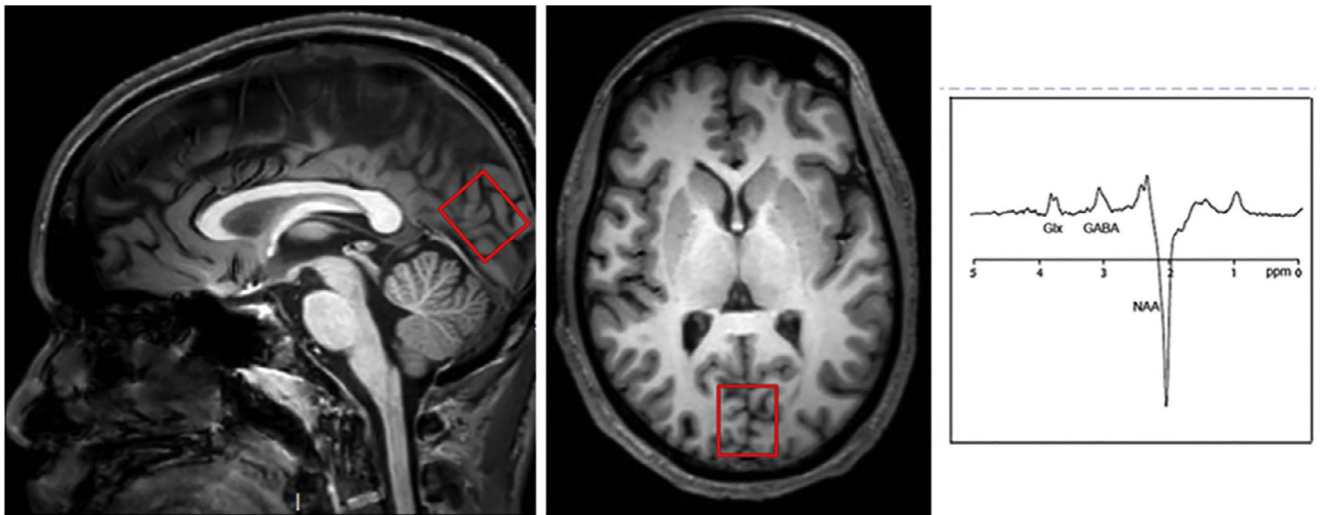


Figure 1.
Left: Axial and sagittal T1-weighted images showing location of ^1H -MRS voxel placements for the occipital cortex. Right: representative ^1H -MRS MRS spectrum in the occipital cortex. Chemical shifts are indicated in parts per million (ppm). GABA is at 3.0 ppm.

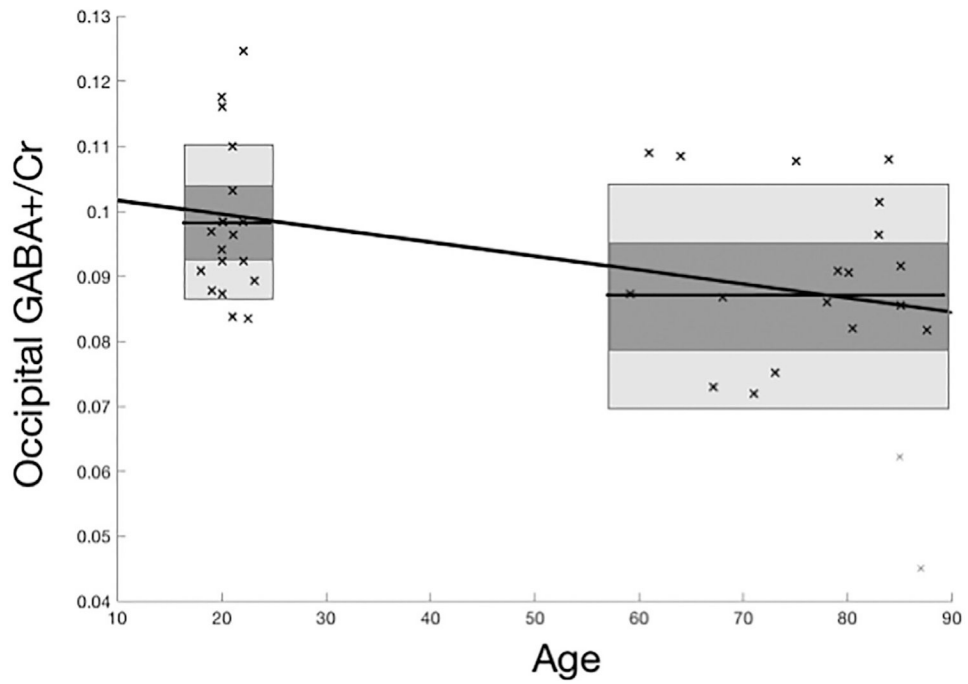


Figure 2. Effect of age group on occipital GABA+/Cr ratios in occipital GABA concentrations in young (18–23 years old) and older (59–87 years old) participants. A lower GABA +/Cr ratio is seen in older participants. Horizontal line across the box marks the mean, dark gray area corresponds to 95% confidence interval, light gray area is standard deviation.

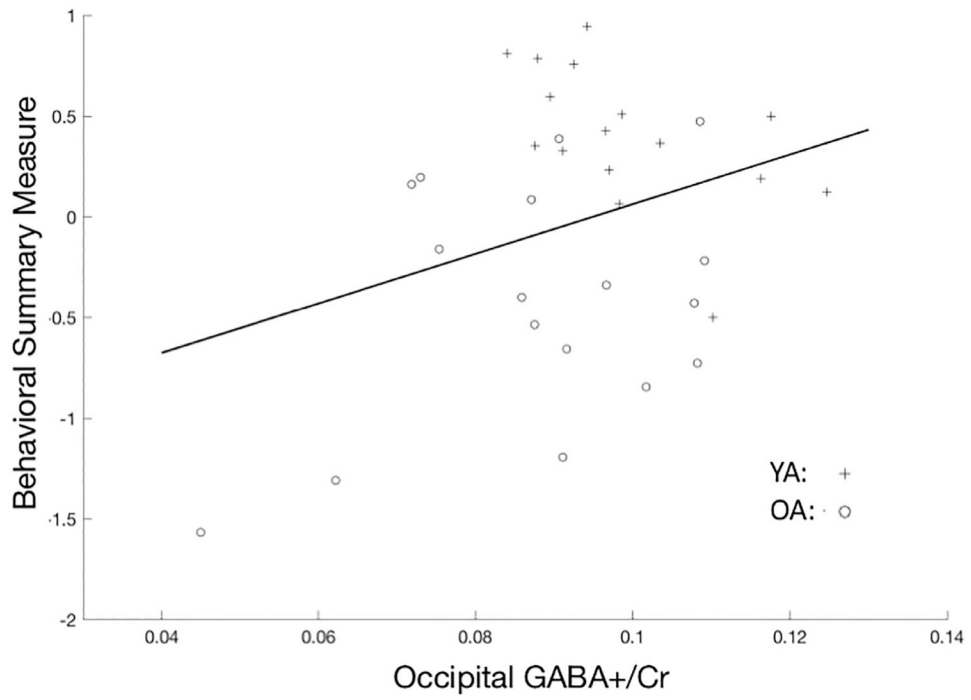


Figure 3. Relationship between occipital GABA+/Cr ratios (*x* axis) and scores on the summary measure extracted by *z* scoring and averaging behavioral performance on 11 tasks (*y* axis). Higher GABA+/Cr ratios are associated with better behavioral performance. OA, older adults; YA, young adults.

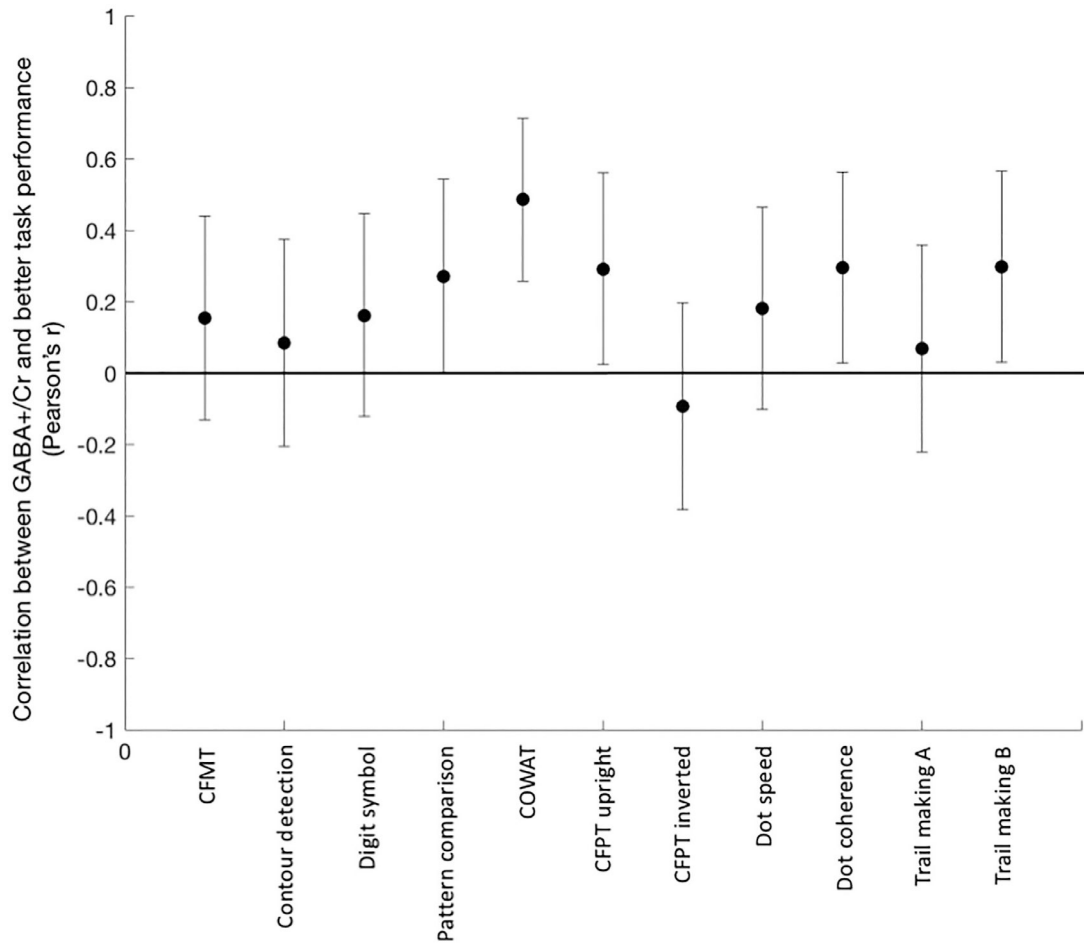


Figure 4. Correlations between occipital GABA+/Cr ratios and performance (*y* axis) on each of 11 behavioral tasks (*x* axis). Correlations on tasks in which better performance is associated with lower scores are flipped, so that for all tasks, a positive correlation indicates better performance is associated with higher GABA+/Cr ratios. Positive correlations were found for ten out of 11 tasks. CFMT, Cambridge face memory test; CFPT, Cambridge face perception test; COWAT, controlled oral word association test.

TABLE 1.

Demographic Characteristics of Young Adult and Older Adult Groups, and Group Differences As Determined by Two-Sample *t* Tests.

	Young Adults (n = 17)		Older Adults (n = 18)		Group Difference	
	Mean	SD	Mean	SD	t ₃₇	p
Age	20.74	1.37	76.50	8.73	27.50	<0.001
MMSE	29.42	0.69	29.35	1.14	0.23	0.82
ERVT	19.71	6.17	31.35	10.29	4.26	<0.001

ERVT, extended range vocabulary test; MMSE, Mini-Mental State Exam.

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TABLE 2.
Average Occipital Metabolite Ratios in Young Adult and Older Adult Groups, and Group Differences As Assessed by One-Tailed, Two-Sampled *t* Tests.

	Young Adults		Older Adults		Group Difference		
	Mean	SD	Mean	SD	df	t	p (one-tailed)
GABA+/Cr	0.10	0.01	0.09	0.01	33	2.22	<0.05
Myo/Cr	0.60	0.06	0.53	0.13	36	2.00	0.05
Cho/Cr	0.16	0.01	0.16	0.02	36	-0.42	n.s.*
NAA/Cr	1.49	0.11	1.39	0.09	36	3.03	<0.01
Glx/Cr	1.61	0.18	1.52	0.23	36	1.45	0.07

Cho, choline; Cr, creatine; GABA, gamma-aminobutyric acid; Glx, glutamate and glutamine; Myo, myoinositol; NAA, N-acetylaspartic acid.

* Nonsignificant. Direction of effect was opposite to that predicted, and thus a one-tailed *t* test was not conducted.

TABLE 3.
Performance on Behavioral Tasks, Group Differences As Assessed by One-Tailed, Two-Sample *t* Tests and Correlations Between Behavioral Performance and GABA Concentration.

	Young Adult Group (n = 17)		Older Adult Group (n = 18)		Group Difference <i>t</i>	<i>p</i> (one-tailed)	Correlation with GABA (Across All Participants)	
	Mean	SD	Mean	SD			<i>R</i>	<i>p</i> (one-tailed)
Better performance higher								
CFMT	76.32	10.83	66.34	10.92	2.98	<0.001	0.15	0.20
Contour detection	43.27	7.26	36.19	4.39	3.83	<0.001	0.08	0.32
Digit symbol	73.57	15.20	50.29	9.38	5.98	<0.001	0.16	0.18
Pattern comparison	22.62	3.10	14.60	2.58	9.11	<0.001	0.27	0.06
COWAT	44.76	9.85	42.29	13.66	0.67	0.25	0.49	<0.01
Better performance lower								
CFPT upright	4.22	1.11	5.62	1.94	-2.86	<0.001	-0.29	<0.05
CFPT inverted	7.94	2.22	8.70	1.28	-1.37	0.09	0.09	n.s.*
Dot Speed	23.26	10.38	28.78	11.69	-1.62	0.06	-0.18	0.16
Dot Coherence	38.23	12.68	48.48	23.09	-1.78	<0.05	-0.30	<0.05
Trail making A	22.97	6.51	34.19	10.20	-4.25	<0.001	-0.07	0.35
Trail making B	50.34	12.85	82.96	38.09	-3.72	<0.001	-0.30	<0.05

CFMT, Cambridge face memory test; CFPT, Cambridge face perception test; COWAT, controlled oral word association test; GABA, gamma-aminobutyric acid.

* Nonsignificant. Relationship between task performance and GABA levels was opposite to that predicted, and so exact significance values were not calculated.

Regressions Between Behavioral Summary Measure of Fluid Processing and Occipital Metabolite Ratios.

TABLE 4.

	Full Sample			Young Adult Group			Older Adult Group		
	df	T	p (one tailed)	df	T	p (two tailed)	df	T	p (two tailed)
GABA+/Cr	31	1.84	0.07	14	-2.45	<0.05	15	1.47	0.16
Myo/Cr	34	2.70	0.01	16	0.69	0.85	16	1.28	0.22
Cho/Cr	34	-0.16	n.s.*	16	-1.52	0.15	16	0.86	0.40
NAA/Cr	34	1.87	0.07	16	-0.08	0.94	16	-0.04	0.97
Glx/Cr	34	3.36	<0.01	16	0.27	0.79	16	3.34	<0.01

Cho, choline; Cr, creatine; GABA, gamma-aminobutyric acid; Glx, glutamate and glutamine; Myo, myoinositol; NAA, N-acetylaspartic acid.

* Nonsignificant. Relationship between task performance and metabolite ratios was opposite to that predicted, and so exact significance values were not calculated.