Frontal Lobe γ-Aminobutyric Acid Levels During Adolescence: Associations with Impulsivity and Response Inhibition

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Background: The brain undergoes major remodeling during adolescence, resulting in improved cognitive control and decision-making and reduced impulsivity, components of behavior mediated in part by the maturing frontal lobe. γ-Aminobutyric acid (GABA), the main inhibitory neurotransmitter system, also matures during adolescence, with frontal lobe GABA receptors reaching adult levels late in adolescence. Thus, the objective of this study was to characterize in vivo developmental differences in brain GABA levels.

Methods: Proton magnetic resonance spectroscopy was used at 4 T to acquire metabolite data from the anterior cingulate cortex (ACC) and the parieto-occipital cortex (POC) in adolescents ($n = 30$) and emerging adults ($n = 20$).

Results: ACC GABA/creatine (Cr) levels were significantly lower in adolescents relative to emerging adults, whereas no age differences were observed in the POC. Lower ACC GABA/Cr levels were significantly associated with greater impulsivity and worse response inhibition, with relationships being most pronounced for ACC GABA/Cr and No-Go response inhibition in adolescent males.

Conclusions: These data provide the first human developmental in vivo evidence confirming frontal lobe GABA maturation, which was linked to impulsiveness and cognitive control. These findings suggest that reduced GABA may be an important neurobiological mechanism in the immature adolescent brain, contributing to the reduced yet rapidly developing ability to inhibit risky behaviors and to make suboptimal decisions, which could compromise adolescent health and safety.

Key Words: ACC, adolescent, GABA, emerging adult, menstrual cycle, MRS

The brain undergoes major remodeling during adolescence (1), including alterations in cerebral structure and function (2,3) that lead to improved cognitive control and decision-making (4,5), as well as reduced impulsivity and risk-taking (6). These behavioral components are mediated in part by the frontal lobe (7–9), which is the last brain region to mature in humans (10). γ-Aminobutyric acid (GABA), the major inhibitory neural system in mammalian brain, also undergoes marked maturation during adolescence (11). Thus, developmental GABA alterations may be involved in age-related improvements on response inhibition tasks, or the ability to "hold back" less optimal or inappropriate responding, mediated in part by the maturing frontal cortex.

In rats, GABA concentrations at birth are 50% of adult levels (12). Glutamic acid decarboxylase (GAD), which catalyzes the decarboxylation of glutamate to GABA and carbon dioxide, and the density of postsynaptic GABA receptors also increase linearly to reach adults levels but lag behind the increase in GABA concentrations (12–14). Given that GABA also plays a prominent role in the metabolism of glucose and fatty acids and is taken up by non-neuronal cells early in development, GABA concentrations may be a more liberal index of GABA development than enzymatic activity or receptor density (12). In non-human primates, chandelier inhibitory interneurons undergo marked developmental increases in terminal density in the prefrontal cortex (PFC), whereas GABA plasma membrane transporters remain stable (15). Postnatal changes in GABA binding are more pronounced in humans, with GABAergic receptor density increasing fivefold during the perinatal period, followed by an additional 100% increase several weeks thereafter (16). $GABA_A$ receptors reach adult levels by age 18 years in frontal cortex and age 19.5 years in the PFC, unlike subcortical structures that reach adult levels earlier (e.g., basal ganglia, age 14 years) (17). In addition, a recent human post mortem study examining expression of interneuron markers in the dorsolateral PFC (DLPFC) provides support that GABAergic neurons continue to differentiate and mature throughout the second decade of life (18).

Recent advances in proton magnetic resonance spectroscopy (^{1}H-MRS) have significantly improved the ability to detect and quantify in vivo brain GABA (19–25). The development of specialized editing techniques was necessary, given that the concentration of GABA is near the lower limit of detection and is obscured by metabolite peaks of higher concentrations, especially creatine (Cr). Low GABA, measured with the use of ^{1}H-MRS, has been observed in a number of pathological conditions in adults including epilepsy, anxiety, depression, obsessive-compulsive disorder, and alcohol and cocaine dependence (26–37). More recently, adolescents with major depressive disorder were reported to have lower GABA in the anterior cingulate cortex (ACC) compared with healthy comparison subjects (38). Importantly, some pharmacologic treatments for these psychiatric and neurological conditions, as well as natural interventions such as yoga, have been reported to increase GABA (39–41).

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Table 1. Demographic and Clinical Data

	ADO ($n = 30$)	EA ($n = 20$)	p
Subject Demographics			
Age	13.6 ± .9	21.6 ± 1.7	.0001
Education	7.3 ± .9	14.7 ± 1.3	.0001
Female	50%	50%	ns
Handedness	27 R, 3 L	20 R, 0 L	-
Ethnicity	87% Caucasian	75% Caucasian	-
Barratt Impulsivity			
Attention	15.3 ± 4.2	14.6 ± 3.4	ns
Motor	24.2 ± 4.1	18.7 ± 2.9	.0001
Non-Planning	26.3 ± 4.8	21.6 ± 4.3	.001
Total score	65.8 ± 10.3	54.8 ± 8.5	.0001

Data represent mean values ± SD.

ADO, adolescent; EA, emerging adult; ns, not statistically significant ($p > .05$).

To date, there are no published developmental data comparing in vivo brain GABA levels in healthy human adolescents with adults. On the basis of previous structural and functional developmental findings (3,4,10,18), the a priori hypotheses of this study were that 12- to 14-year-old adolescents (ADO) would exhibit lower GABA than 18- to 24-year-old emerging adults (EA) in the ACC, but no differences would be observed in a comparison region in the parieto-occipital cortex (POC). There are some published data available relating GABA in the DLPFC to impulsivity and unconscious motor control; however, these reports are limited to adults (42,43). Although investigations of the ACC have failed to show a relationship between GABA and impulsivity in adults, the ACC was chosen for examination in the present study because this region has been implicated in the development of higher-order cognitive processes, including cognitive control, response selection, and decision-making (44–52). Therefore, we hypothesized that lower ACC GABA would predict greater impulsivity on the Barratt Impulsivity Scale and worse response inhibition on Go No-Go (GNG) and Stroop Color-Word tasks in both our subject groups. Given that menstrual cycle phase has been shown to influence GABA (29), an exploratory aim of the study was to investigate the influence of menstrual cycle phase on the research findings.

Methods and Materials

Participants

Participants included 30 healthy ADO (12–14 years, 15 females) and 20 healthy EA (18–24 years, 10 females), with middle-upper class socioeconomic status (53) (Table 1). The clinical research protocol was approved by the Institutional Review Board of McLean Hospital. After complete study description, all subjects and ADO parent(s)/guardian(s) provided written informed assent/consent. Participants completed urine screening before scanning to rule out current psychoactive substance use and pregnancy. Participants were free of psychiatric diagnoses on the basis of Kiddie-Schedule for Affective Disorders and Schizophrenia interviews (ADO) (54) or the Structured Clinical Interview for DSM-IV Non-Patient Edition (EA) (55). Participants had no prior head trauma or loss of consciousness and were free of radiologic brain abnormalities, MR scanning contraindications, or current psychoactive substance use, including nicotine. Fewer than three lifetime episodes of alcohol use and no history of drug use were reported in ADO, and EA average alcohol use was 1.3 ± 1.1 alcoholic drinks on 2.2 ± 1.8 occasions per month. Menstrual cycle status was determined by self-report: 33% of ADO and 60% of EA females were in the follicular phase (cycle days 2–9); 33% of ADO and 30% of EA females were in the luteal phase (cycle days 13–32); 20% of ADO females had not yet begun cycling; and in 14% of ADO and 10% of EA, menstrual cycle information was unavailable.

Clinical and Cognitive Measures

Subjects completed the Barratt Impulsiveness Scale (BIS-11) (56,57), a self-report measure of impulsivity yielding a total score for trait impulsivity, and subscale impulsivity scores: attention (rapid shifts in attention/impatience with complexity), motor (impetuous action), and non-planning (lack of future orientation). The adult and adolescent BIS-11 each consist of 30 questions, with 14 identical questions and 16 questions age-appropriately modified (e.g., adolescent: "I change my mind about what I will do when I grow up"; adult: "I change jobs"). Versions were scored by use of the identical procedure, and internal consistency was similar between groups: Cronbach's $\alpha = .696$ and .708, ADO and EA, respectively.

The Wechsler Abbreviated Scale of Intelligence (58) vocabulary subtest was administered to obtain an estimate of general intelligence. The California Verbal Learning test [CVLT-C, adolescent (59); CVLT-II, adult (60)] was used to assess working memory/auditory attention span, verbal learning and memory and verbal recognition (Table 2). A modified Stroop test (61) was used to assess inhibition of inappropriate responses and resisting interference with the use of three subtests: Color Naming (CN),

Table 2. Cognitive Performance Data

	ADO ($n = 30$)	EA ($n = 20$)	p
WASI			
Vocabulary T-score	62.2 ± 9.6	61.7 ± 7.3	ns
	ADO ($n = 30$)	EA ($n = 19$)[a]	p
CVLT-C/CVLT-II			
Trial 1 (% correct)	51.1 ± 11.0	52.0 ± 16.3	ns
Trials 1– 5 (% correct)	73.3 ± 9.3	75.4 ± 11.5	ns
Recognition (% correct)	95.6 ± 7.7	98.0 ± 3.0	ns
	ADO ($n = 30$)	EA ($n = 20$)	p
Stroop Color-Word Task			
Color naming time (sec)	67.4 ± 11.0	56.8 ± 10.2	.001
Errors	2.3 ± 1.7	1.1 ± 1.1	.007
Word reading time (sec)	51.8 ± 8.1	45.1 ± 7.6	.005
Errors	1.3 ± 1.2	1.3 ± 1.2	ns
Interference time (sec)	120.2 ± 28.9	103.4 ± 28.3	.047
Errors	4.4 ± 4.0	3.0 ± 2.5	ns
Derived interference time (sec)	52.8 ± 21.4	46.6 ± 24.4	ns
	ADO ($n = 30$)	EA ($n = 18$)[b]	p
Go No-Go Task			
Go total percent accuracy	90.6 ± 4.8	95.4 ± 4.4	.001
Go reaction time (msec)	412.6 ± 77.0	397.5 ± 81.8	ns
No-Go total percent accuracy	71.1 ± 15.8	87.9 ± 6.2	.0001

Data represent mean scores ± standard deviation.

ADO, adolescent; EA, emerging adult; ns, not statistically significant ($p > .05$); WASI, Wechsler Abbreviated Scale of Intelligence; CVLT, California Verbal Learning Task.

[a]CVLT data were unavailable from one EA subject.

[b]Data from two EA subjects for No-Go trials were determined to be statistical outliers and were not included in the univariate analyses of variance.